

HJD
PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668,669)
Issued: May 26, 1987)
To: Jean-Claude Barriere, Claude Cotrel,)
Jean-Marc Paris)
Assignee: Rhone-Poulenc Rorer S.A.)
For: PRISTINAMYCIN II_B DERIVATIVES)
AND COMPOSITIONS CONTAINING)
THEM)

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OFFICE OF PETITIONS
DEPUTY A/C PATENTS

RECEIVED
NOV 10 1999
PATENT EXTENSION
A/C PATENTS

ATTN: BOX PATENT EXT.
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

**APPLICATION FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. § 156**

Your Applicant, Rhone-Poulenc Rorer S.A., represents that it is the Assignee of the entire interest in and to Letters Patent of the United States 4,668,669 granted to Jean-Claude Barriere, Claude Cotrel, and Jean-Marc Paris on the 26th day of May, 1987, for PRISTINAMYCIN II_B DERIVATIVES AND COMPOSITIONS CONTAINING THEM, by virtue of an assignment in favor of Rhone-Poulenc Rorer S.A. The assignment to Rhone-Poulenc Sante was recorded on Reel 4504, at Frame 063, on January 10, 1986, and the name change to Rhone-Poulenc Rorer S.A. was submitted to the Patent and Trademark Office for recordation on October 5, 1999. (Attachment A)

LAW OFFICES
MCNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
202-408-4000

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In re U.S. Patent No. 4,668,669
Attorney Docket No. 3804.0055

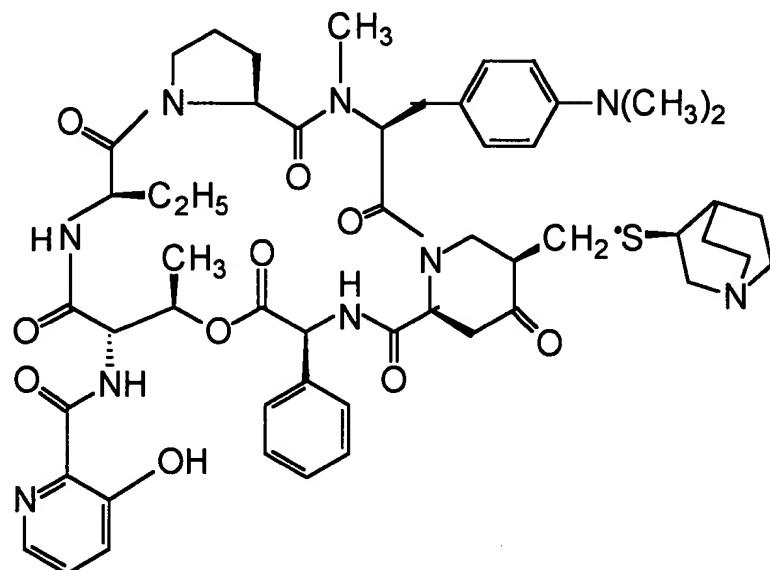
By the Power of Attorney enclosed herein (Attachment B), Applicant appoints attorneys in Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., including Charles E. Van Horn, as attorney for Rhone-Poulenc Rorer S.A. with regard to this application for extension of the term of U.S. Patent 4,668,669 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application is presented in a format that follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

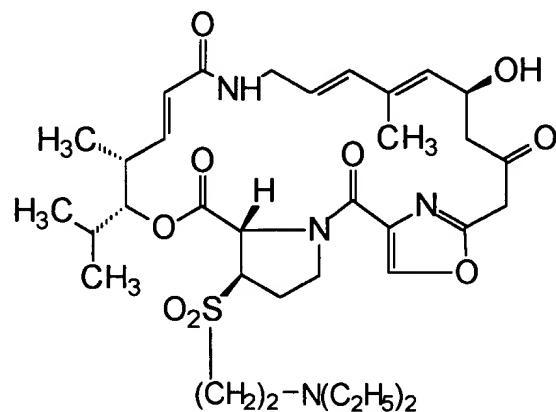
(1) The approved product SYNERCID® is an association of 2 semisynthetic pristinamycin derivatives in a weight ratio of 30/70. The chemical names for the 2 semisynthetic pristinamycin derivatives are 5δR-[(3S)-3-quinuclidinyl]thiomethyl pristinamycin I_A (quinupristin) and 26R-[(2-diethylaminoethyl)sulfonyl]pristinamycin II_B (dalfopristin). The formulation including SYNERCID® is available in a sterile non-pyrogen freeze dried preparation which contains quinupristin and dalfopristin as their methane sulfonic salts.

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Quinupristin has the structural formula:



Dalfopristin has the structural formula:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505.

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(3) The approved product SYNERCID® received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on September 21, 1999.

(4) The active ingredients in SYNERCID® are the methane sulfonate salts of 5δR-[(3S)-3-quinuclidinyl]thiomethyl pristinamycin I_A (quinupristin) and 26R-[(2-diethylaminoethyl)sulfonyl]pristinamycin II_B (dalfopristin), which, on information and belief, have not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 50-747 for SYNERCID® by the Food and Drug Administration on September 21, 1999. A copy of the insert describing the approved product is attached (Attachment C).

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period will expire on November 19, 1999.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Jean-Claude Barriere, Claude Cotrel and Jean-Marc Paris

Patent No.: 4,668,669

Issue Date: May 26, 1987

Expiration Date: January 10, 2006 (by virtue of the patent term
resetting provisions of 35 U.S.C. § 154(c)(1) enacted
under the URAA).

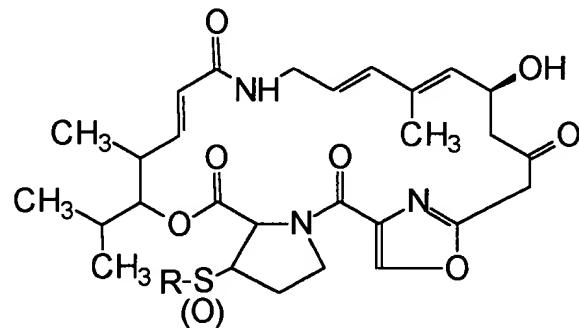
In re U.S. Patent No. 4,668,669
Attorney Docket No. 3804.0055

(7) A true copy of the patent is attached (Attachment D).

(8) No terminal disclaimer or reexamination certificate has been issued on this patent. A request for a certificate of correction as filed on November 2, 1999, is attached (Attachment E). A copy of the maintenance fee statement indicating payment of maintenance fees in 1990, 1994 and 1998 is attached (Attachment F).

(9) U.S. Patent 4,668,669 claims an active ingredient in the approved product in at least claims 1, 2, 5 (as corrected), and 9, and a method of using an active ingredient in claim 10. Claims 1, 2, 5 (as corrected), 9 and 10 claim at least one active ingredient in SYNERCID® as follows:

1. A pristinamycin II_B of the formula:



in which R denotes

either a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidinyl or 3- or 4-azepinyl radical each of which is unsubstituted or substituted by alkyl,
or alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms,

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alkylamino, dialkylamino, and dialkylcarbamoyloxy, the alkyl moieties of the said dialkylamino and dialkylcarbamoyloxy radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, and, if required, an oxygen, sulphur, or other nitrogen atom, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, 1-azepinyl, morpholino, thiomorpholino in the form of sulphoxide or sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-1-homopiperazinyl or imidazolyl radical, all of which may be unsubstituted or substituted by alkyl, or R denotes an alkyl of 2 to 4 carbon atoms substituted by 2- or 3-azetidinyl, 2- or 3-pyrroliidinyl, 2-, 3- or 4-piperidyl, 2- 3- or 4-azepinyl, piperazinyl, 4-alkyl-piperazinyl, quinolyl, isoquinolyl, or imidazolyl radical, each of which is unsubstituted or substituted by alkyl, these heterocyclic rings being linked to the alkyl of 2 to 4 carbon atoms by a carbon atom of the ring, n is 1 or 2 and, unless stated otherwise, the abovementioned alkyl radicals are linear or branched and contain 1 to 10 carbon atoms each, in its isomeric forms or their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

Claim 1 reads on an active ingredient in SYNERCID®, specifically the pharmaceutically acceptable methane sulfonate salt of dalfopristin, when R is an alkyl of 2 carbon atoms substituted by dialkylamino.

2. A pristinamycin II_B according to claim 1, wherein R denotes alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 5 or 6 ring atoms, N-alkyl-N-cycloalkylamino of 5 or 6 ring atoms, alkylamino of 1 to 4 carbon atoms, or dialkylamino in which each alkyl is of 1 to 3 carbon atoms or the

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alkyls form, with the nitrogen atom to which they are attached, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, or 1-azepinyl radical, or R denotes a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidyl or 3- or 4-azepinyl radical each of which is unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the said alkyl being in a 1- or a 2-position, in its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

Claim 2 likewise is directed to an active ingredient in SYNERCID®, specifically the pharmaceutically acceptable methane sulfonate salt of dalfopristin, when R is an alkyl of 2 carbons substituted by dialkylamino where each alkyl has two carbon atoms.

5. A pristinamycin II_B according to claim 1 which is 26-(2-diethylaminoethyl)sulphonylpirstinamycin II_B, its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

Claim 5 (as corrected by the request for certificate of correction) is directed to an active ingredient in SYNERCID®, specifically the pharmaceutically acceptable methane sulfonate salt of dalfopristin.

9. A pharmaceutical composition comprising an effective amount of a pristinamycin II_B according to claim 1 in association with a compatible pharmaceutically acceptable carrier and/or adjuvant.

Claim 9 reads on an active ingredient SYNERCID® since the active ingredient methane sulfonic salt of dalfopristin is a pharmaceutically acceptable acid additive salt of a pristinamycin II_B according to claim 1.

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10. Method of controlling bacterial growth which comprises exposing said bacteria to the effect of a pristinamycin II_B according to claim 1 in sufficient concentration to control said bacteria.

Claim 10 reads on a method of using an active ingredient in SYNERCID® since it reads on exposing bacteria to the effect of a pharmaceutically acceptable acid additive salt of a pristinomycin II_B according to claim 1, which covers the active ingredient methane sulfonic salt of dalfopristin.

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(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

Investigational New Drug Application (IND 45304) for SYNERCID® was filed May 24, 1994, and became effective on June 23, 1994, 30 days after the date of submission on May 24, 1994.

New Drug Application for SYNERCID® (NDA 50-747) was submitted on September 5, 1997.

New Drug Application for SYNERCID® was approved on September 21, 1999

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(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to SYNERCID® and the dates applicable to these significant activities are set forth in a chronology of events in Attachment G.

LAW OFFICES
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202-408-4000

In re U.S. Patent No. 4,668,669
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(12)(i) Applicant is of the opinion that U.S. Patent 4,668,669 is eligible for extension of the patent term under 35 U.S.C. § 156 because it satisfies all requirements for such extension as follows:

- (a) 35 U.S.C. § 156(a) - U.S. Patent 4,668,669 claims the product SYNERCID®.
- (b) 35 U.S.C. § 156(a)(1) - U.S. Patent 4,668,669 has not expired before submission of this application.
- (c) 35 U.S.C. § 156(a)(2) - The term of U.S. Patent 4,668,669 has never been extended under 35 U.S.C. § 156(e)(1).
- (d) 35 U.S.C. § 156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.
- (e) 35 U.S.C. § 156(a)(4) - The product SYNERCID® has been subjected to a regulatory review period before its commercial marketing or use.
- (f) 35 U.S.C. § 156(a)(5)(A) - The commercial marketing or use of the product SYNERCID® after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (i.e., Section 505) under which such regulatory review period occurred.
- (g) 35 U.S.C. § 156(c)(4) - No other patent has been extended for the same regulatory review period for the product SYNERCID®.

LAW OFFICES

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202-408-4000

In re U.S. Patent No. 4,668,669
Attorney Docket No. 3804.0055

(12)(ii) The length of the extension of patent term of U.S. Patent 4,668,669 claimed by Applicant is that period authorized by 35 U.S.C. § 156(c) which has been calculated to be 1333 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on June 23, 1994 and ended September 21, 1999, which is a total of 1918 days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", began on June 23, 1994 and ended on September 5, 1997, which is 1171 days; and

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Approval Period", began on September 5, 1997, and ended on September 21, 1999, which is a total of 747 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (1918 days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (May 26, 1987) which is zero (0) days; and

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

In re U.S. Patent No. 4,668,669
Attorney Docket No. 3804.0055

(3) One-half the number of days determined in sub-paragraph (12)(ii)(a)(1) above after the patent issued (one-half of 1171 days) which is 585 days;

(c) The number of days as determined in sub-paragraph (12)(ii)(b) (1333 days) when added to the expiration date of the original term of the patent (January 10, 2006) would result in the date of September 4, 2009

(d) Fourteen (14) years when added to the date of the NDA approval (September 21, 1999) would result in the date of September 21, 2013;

(e) The earlier date as determined in sub-paragraphs (12)(ii)(c) and (12)(ii)(d) is September 4, 2009;

(f) Since U.S. Patent 4,668,669 issued after September 24, 1984, the period of extension may not exceed five years from the original expiration date of January 10, 2006. Five years when added to the original expiration date of the patent would result in the date of January 10, 2011.

(g) The earlier dates as determined by sub-paragraph (12)(ii)(e) and (12)(ii)(f) is September 4, 2009.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

In re U.S. Patent No. 4,668,669
Attorney Docket No. 3804.0055

(14) The prescribed fee for receiving and acting upon this application is attached as a check in the amount of \$1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 06-0916.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Charles E. Van Horn

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

1300 I Street, N.W.

Washington, D.C. 20005-3315

Phone: 202-408-4000

Fax: 202-408-4400

(16) Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof (Attachment H).

LAW OFFICES
FINNEMAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
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WASHINGTON, D.C. 20005
202-408-4000

In re U.S. Patent No. 4,668,669
Attorney Docket No. 3804.0055

(17) The requisite declaration pursuant to 37 C.F.R. § 1.740(b) is attached
(Attachment I).

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

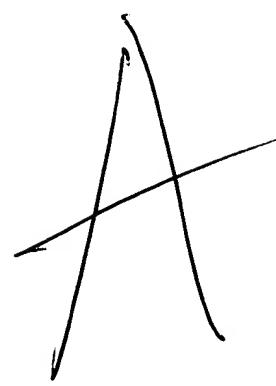
By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: November 10, 1999

Attachments:

Notification of Change of Name/Address of Assignee (Attachment A)
Power of Attorney (Attachment B)
Package Insert for SYNERCID® (Attachment C)
U.S. Patent 4,668,669 (Attachment D)
Copy of Request for Certificate of Correction (Attachment E)
Copy of Maintenance Fee Statement (Attachment F)
Chronology of Regulatory Review Period (Attachment G)
Certification of Copies of Application Papers (Attachment H)
Declaration Pursuant to 37 C.F.R. § 1.740(b) (Attachment I)

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
202-408-4000



CEV

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In re U.S. Patent No. 4,668,669

Inventors: Jean-Claude Barriere et al.

Issued: May 26, 1987

Title: PRISTINAMYCIN II_B DERIVATIVES AND COMPOSITIONS
CONTAINING THEM

ATTN: BOX ASSIGNMENTS

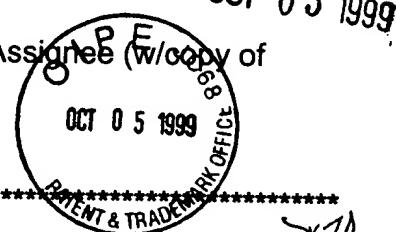
Enclosed:

1. Notification of Change of Address of Assignee (w/copy of
executed translator's declaration)
2. Form PTO 1595
3. Check for \$40.00

Date: 10/05/99

Case Ref.: 3804.0055

CEVanHorn/C. Woods (Drop 701)



To the Honorable Commissioner of Patents and Trademarks:
Please record the attached original documents or copy thereof.

ATTN. BOX ASSIGNMENTS

1. Name of conveying party(ies):

Rhône-Poulenc Sante

2. Name and address of receiving party(ies):

Name: Rhône-Poulenc Rorer S.A.

Additional names(s) of conveying party(ies)
attached? Yes No

Internal Address:

3. Nature of conveyance:

Assignment Merger
 Security Agreement Change of Name
 Other _____

Street Address: 20 avenue Raymond Aron

Execution Date: December 27, 1990

City: ANTONY

Cntry: France ZIP: 92160

Additional name(s) & address(es) attached?
 Yes No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

B. Patent No.(s)

4,668,669

Additional numbers attached? Yes No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Internal Address: _____

Street Address: 1300 I Street, N.W.
Suite 700

City: Washington, D.C.

State: _____ ZIP: 20005-3315

6. Total number of applications and patents involved 17. Total fee (37 CFR 3.41): \$ 40.00 Enclosed Authorized to be charged to
deposit account 06-09168. Deposit account number: 06-0916

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct,
and any attached copy is a true copy of the original document.

Charles E. Van Horn, Reg. No. 40,266

Name of Person Signing

Signature

Date

Total number of pages including cover sheet, attachments and document: 11

PATENT
Atty. Docket No. 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:)
Jean-Claude BARRIERE et al.)
Patent No.: 4,668,669)
Issued: May 26, 1987) **ATTN: BOX ASSIGNMENTS**
Title: PRISTINAMYCIN II_B DERIVATIVES)
AND COMPOSITIONS CONTAINING)
THEM)
Assignee: Rhône-Poulenc Rorer S.A.)

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

NOTIFICATION OF CHANGE OF NAME/ADDRESS OF ASSIGNEE

It is requested that the records of the Patent and Trademark Office be updated to reflect the Assignee's change of name/address as follows:

RHONE-POULENC RORER S.A.
20 avenue Raymond Aron
92160 ANTONY
FRANCE

The original U.S. patent application Serial No. 817,548 (filed January 10, 1986) was assigned to RHONE-POULENC SANTE, Les Miroirs, 18 avenue d'Alsace, 92400 COURBEVOIE (France). A change of name of RHONE-POULENC SANTE to RHONE-POULENC RORER S.A. was published in The Journal Spécial des Sociétés on

December 29, 1990. A copy of "Proces-Verbal De L'Assemblee Generale Extraordinaire" is attached, along with an executed translator's declaration. The recording fee of \$40.00 (37 C.F.R. § 3.41) is enclosed.

If there are any additional fees due in connection with the filing of this Notification, please charge the fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: October 5, 1999

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
202-408-4000

TRANSLATOR'S DECLARATION

I, Stephen Thomas MOGER BA(Hons),
translator to RWS Translations Ltd., of Europa House, Marsham
Way, Gerrards Cross, Buckinghamshire, England declare:

1. That I am a citizen of the United Kingdom of Great Britain
and Northern Ireland.
2. That I am well acquainted with the French and English
languages.
3. That the attached is an accurate translation of the
accompanying documents in the French language to the best of my
knowledge and belief.

I declare further that all statements made herein of my own
knowledge are true and that all statements made on information
and belief are believed to be true; and further that these
statements were made with the knowledge that willful false
statements and the like so made are punishable by fine or
imprisonment or both, under Section 1001 Title 18 of the United
States Code and that such willful statements may jeopardize the
validity of the application or any patent issuing thereon.

Date: 17 June 1996



Stephen Thomas MOGER

For and on behalf of RWS Translations Ltd.

CERTIFIED TRUE COPY

RHONE-POULENC SANTE

Limited company with capital of F. 692,471,000
Head office: 20, avenue Raymond Aron - ANTONY (92160)
C.R.: Nanterre B 304 463 284

=====

MINUTES
OF THE EXTRAORDINARY GENERAL MEETING
on 27th December 1990

=====

On Thursday 27th December 1990, at 9 a.m., the shareholders of the company RHONE-POULENC SANTE met for an Extraordinary General Meeting at 25 Quai Paul DOUMER - 92408 COURBEVOIE in accordance with the letter of notification to attend which was sent to them, as well as to the auditors, on 12th December 1990.

The Meeting appointed its Board.

Mr Jean-Jacques BERTRAND, Chairman of the Board of Directors, presided over the Meeting.

Mr Hubert de FORCEVILLE, representative of the company RHONE-POULENC CHIMIE
and

Mr Marcel CHEVRIER

the two shareholders with the largest number of votes, who were present and in agreement, were appointed to serve in the capacity of Scrutineers.

Mr Yves BRISSY was appointed to serve in the capacity of

Secretary.

The Chairman stated, according to the attendance list certified accurate by the Members of the Board, that the shareholders who were present or represented owned the entirety of the shares forming the authorized capital.

The Meeting, thus bringing together more than half the authorized capital, was properly constituted and was therefore able to debate validly.

The Chairman tabled and made available to the shareholders:

- 1) a copy of the letter of notification to attend which was sent to each of the shareholders as well as to the Auditors,
- 2) the attendance list,
- 3) the collection of forms for voting by post or by proxy signed by the shareholders,
- 4) the assignment agreements,
- 5) the report of the Board of Directors,
- 6) the reports of the Auditor of the hive-off,
- 7) the draft resolutions,
- 8) the articles of association.

The Chairman then declared that the documents provided for by current legislation had been, as the case may be, either enclosed with the forms for voting by post or by proxy sent to the shareholders or made available to them within the legal time limits.

The Meeting gave him formal acknowledgement of this declaration.

The Chairman then recalled that the Meeting was called for the purpose of discussing the following agenda:

A G E N D A

- Report of the Board of Directors
- Approval of the plan for partial assignment of immovable and movable, tangible and intangible assets appertaining to the "Research and Development" branch of activity carried on at the CRVA and la Croix de Berny sites/Report of the Auditor of the hive-off.
- Approval of the plan for partial assignment of immovable and movable, tangible and intangible assets appertaining to the "Production of Active Principles" branch of activity carried on at Vitry and Villeneuve la Garenne/Report of the Auditor of the hive-off.
- Amendment of the name of the company forming the subject of article 2 of the Articles of Association of the Company.
- Powers

The Chairman then had the report of the Board of Directors read out, the text of which follows:

THIRD RESOLUTION

The General Meeting, having examined the reports of the Board of Directors, decided to modify the name of the Company which became "RHONE-POULENC RORER SA".

Consequently, article 2 of the articles of association was from then on worded as follows:

- Article 2 - Name of the Company

The name of the Company is:

RHONE-POULENC RORER SA

This resolution was carried unanimously.

CERTIFIED TRUE COPY
Chairman and Managing Director
per pro
{signature}

EXTRAIT CERTIFIÉ CONFORME

RHONE-POULENC SANTE
Société anonyme au capital de F. 692 471 000
Siège social : 20, avenue Raymond Aron - ANTONY (92160)
R.C.S. : Nanterre B 304 463 284

PROCES-VERBAL
DE L'ASSEMBLEE GENERALE EXTRAORDINAIRE
du 27 Décembre 1990

Le Jeudi 27 Décembre 1990, à 9 heures, Messieurs les Actionnaires de la Société RHONE-POULENC SANTE se sont réunis en Assemblée Générale Extraordinaire au 25 Quai Paul DOUMER - 92408 COURBEVOIE, conformément à la lettre de convocation qui leur a été adressée, ainsi qu'aux Commissaires aux Comptes, le 12 Décembre 1990.

L'Assemblée procède à la composition de son bureau.

Monsieur Jean-Jacques BERTRAND, Président du Conseil d'Administration, préside l'Assemblée.

et Monsieur Hubert de FORCEVILLE, représentant la Société RHONE-POULENC CHIMIE
Monsieur Marcel CHEVRIER

les deux actionnaires disposant du plus grand nombre de voix, présents et acceptant, sont appelés à remplir les fonctions de Scrutateurs.

Monsieur Yves BRISSY est désigné pour remplir les fonctions de Secrétaire.

Le Président constate, d'après la feuille de présence certifiée exacte par les Membres du bureau, que les actionnaires présents ou représentés possèdent la totalité des actions composant le capital social.

L'Assemblée, réunissant ainsi plus de la moitié du capital social, est régulièrement constituée et peut donc valablement délibérer.

Le Président dépose sur le bureau et met à la disposition des actionnaires :

- 1°) un exemplaire de la lettre de convocation adressée à chacun des actionnaires ainsi qu'aux Commissaires aux Comptes,
- 2°) la feuille de présence,
- 3°) le recueil des formulaires de vote par correspondance ou par procuration signés par les actionnaires,
- 4°) les traités d'apport
- 5°) le rapport du Conseil d'Administration,
- 6°) les rapports du commissaire à la scission
- 7°) le projet de résolutions,
- 8°) les statuts.

Puis, le Président déclare que les documents prévus par la législation en vigue ont été, selon le cas, soit joints aux formulaires de vote, par correspondance par procuration, adressés aux actionnaires, soit tenus à leur disposition dans les délais légaux.

L'Assemblée lui donne acte de cette déclaration.

Puis, Monsieur le Président rappelle que l'Assemblée est réunie en vue de délibérer sur l'ordre du jour suivant :

O R D R E D U J O U R

- Rapport du Conseil d'Administration
- Approbation du projet d'apport partiel d'actif des éléments immobiliers et mobiliers, corporels et incorporels dépendant de la branche d'activité "Recherche et Développement" exploitée sur les sites du CRVA et de la Croix de Berny/Rapport du Commissaire à la scission.
- Approbation du projet d'apport partiel d'actif des éléments immobiliers et mobiliers, corporels et incorporels dépendant de la branche d'activité "Production de Principes Actifs" exploitée à Vitry et Villeneuve la Garenne/Rapport du Commissaire à la scission.
- Modification de la dénomination sociale faisant l'objet de l'article 2 des Statuts de la Société.
- Pouvoirs

.....

TROISIEME RESOLUTION

L'Assemblée Générale, après avoir pris connaissance des rapports du Conseil d'Administration, décide de modifier la dénomination sociale de la Société qui devient "RHONE-POULENC RORER SA".

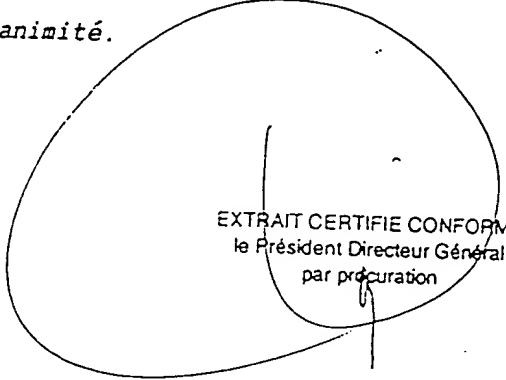
En conséquence l'article 2 des statuts est dorénavant rédigé comme suit :

- Article 2 - Dénomination sociale

La Société a pour dénomination :

RHONE-POULENC RORER SA

Cette résolution est adoptée à l'unanimité.



EXTRAIT CERTIFIÉ CONFORME
le Président Directeur Général
par procuration

K

PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668,669)
Issued: May 26, 1987)
To: Jean-Claude Barriere, Claude Cotrel,
Jean-Marc Paris)
Assignee: Rhone-Poulenc Rorer S.A.)
For: PRISTINAMYCIN II_g DERIVATIVES
AND COMPOSITIONS CONTAINING
THEM)

ATTN: BOX PATENT EXTENSION
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

POWER OF ATTORNEY

Rhone-Poulenc Rorer S.A. is the Assignee of the entire right, title, and interest in
the patent identified above by virtue of an assignment recorded in the Patent and
Trademark Office at Reel 4505, at Frame 063 on January 10, 1986, and name change
submitted to the Patent and Trademark Office for recordation on October 5, 1999.

Assignee, Rhone-Poulenc Rorer S.A., being the owner of the above-identified
U.S. Letters Patent, hereby grants the power of attorney to **FINNEGAN, HENDERSON,**
FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291;
Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R.
Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV,
Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Heftner, Reg. No.

20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewis, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanko Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M.

Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; and James B. Monroe, Reg. No. 33,971, both jointly and separately to be attorneys for Rhone-Poulenc Rorer S.A. with regard to an application for extension of the term of U.S. Patent 4,668,669 and to transact all business in the Patent and Trademark Office connected therewith.

The undersigned is empowered to act on behalf of the Assignee.

Please send all future correspondence concerning the above matter to Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., at the following address:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

RHONE-POULENC RORER S.A.

Date: November 4, 1999

Françoise Lobjois
Name: Françoise Lobjois

Title: Executive

C

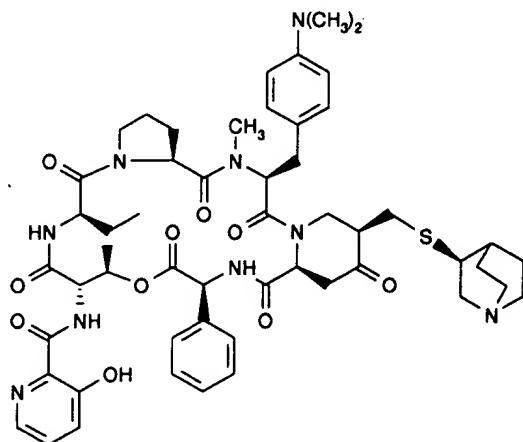
Synercid® (quinupristin-dalfopristin) IV

DESCRIPTION

Synercid® (quinupristin/dalfopristin) I.V., a streptogramin antibacterial agent for intravenous administration, is a sterile freeze-dried formulation of two semisynthetic pristinamycin derivatives, quinupristin (derived from pristinamycin I) and dalfopristin (derived from pristinamycin IIA) in the ratio of 30:70 (w/w).

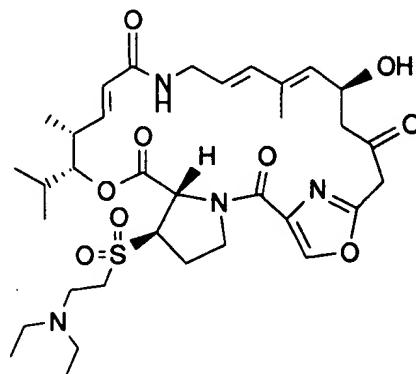
Quinupristin is a white to very slightly yellow, hygroscopic powder. It is a combination of three peptide macrolactones. The main component of quinupristin (>88.0%) has the following chemical name: N-[*(6R,9S,10R,13S,15aS,18R,22S,24aS)*-22-*[p*-(dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-*[[*(3*S*)-3-quinuclidinylthio]methyl]-12*H*-pyrido[2,1-*f*]pyrrolo-[2,1-*I*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide.

The main component of quinupristin has an empirical formula of C₅₃H₆₇N₉O₁₀S, a molecular weight of 1022.24 and the following structural formula:



Dalfopristin is a slightly yellow to yellow, hygroscopic, powder. The chemical name for dalfopristin is: (3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26*aS*)-26-*[[*(2-(diethylamino)ethyl]sulfonyl]-8,9,14,15,24,25,26,26*a*-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]-dioxadiazacyclotetrasine-1,7,16,22(4*H*,17*H*)-tetrone.

Dalfopristin has an empirical formula of C₃₄H₅₀N₄O₉S, a molecular weight of 690.85 and the following structural formula:



Synercid is supplied as a sterile freeze-dried preparation of quinupristin and dalfopristin mesylate for injection in 500 mg single-dose vials.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Quinupristin and dalfopristin are the main active components circulating in plasma in human subjects. Quinupristin and dalfopristin are, however, rapidly converted to several major metabolites: two conjugated metabolites for quinupristin (one with glutathione and one with cysteine) and one non-conjugated for dalfopristin (formed by drug hydrolysis). *In vitro* synergism of quinupristin's metabolites with dalfopristin, and of dalfopristin's metabolite with quinupristin, has been demonstrated. (See Microbiology.)

Pharmacokinetic profiles of quinupristin and dalfopristin in combination with their metabolites were determined using bioassay following multiple 60-minute infusions of Synercid in two groups of healthy young male volunteers. Each group received 7.5 mg/kg intravenously q12h or q8h for a total of 9 and 10 doses, respectively. The pharmacokinetic parameters were comparable with q12h or q8h dosing; those of the q8h regimen are shown in the following table:

Mean Steady-State Pharmacokinetic Parameters of Quinupristin and Dalfopristin in Combination with their Metabolites (\pm SD¹) n=10

	C _{max} ² (μ g/mL)	AUC ³ (μ g.h/mL)	t _{1/2} ⁴ (hr)
Quinupristin and metabolites	3.20 \pm 0.67	7.20 \pm 1.24	3.07 \pm 0.51
Dalfopristin and metabolite	7.96 \pm 1.30	10.57 \pm 2.24	1.04 \pm 0.20

¹ SD = Standard Deviation

² C_{max} = Maximum drug plasma concentration

³ AUC = Area under the drug plasma concentration-time curve

⁴ t _{1/2} = Half-life

The clearances of unchanged quinupristin and dalfopristin are similar (0.7 L/h/kg), and the apparent volume of distribution for both products is approximately 1.0 L/kg. The elimination half-life of quinupristin and dalfopristin is approximately 0.9 and 0.75 hours, respectively.

The protein binding ranges from 55 to 78% for quinupristin and from 11 to 26% for dalfopristin.

Penetration of unchanged quinupristin and dalfopristin in noninflammatory blister fluid corresponds to about 19% and 11% of that estimated in plasma, respectively. The penetration into blister fluid of quinupristin and dalfopristin in combination with their major metabolites was in total approximately 40% compared to that in plasma.

Radiolabeled quinupristin and dalfopristin were shown to penetrate into *ex vivo* human macrophages with ratios of intracellular to extracellular concentrations of 60:1 for quinupristin and 30:1 for dalfopristin after 1 hour. A slow release from macrophages was complete at 5 hours for both quinupristin and dalfopristin.

In a mouse model of *Streptococcus pneumoniae*, Synercid penetration into the lung was demonstrated.

In a rabbit model of *Streptococcus pneumoniae* meningitis, a pharmacodynamic effect of intravenous Synercid was demonstrated, but pharmacokinetic data were not collected.

In vitro, the transformation of the parent drugs into their major active metabolites occurs by non-enzymatic reactions and is not dependent on cytochrome-P450 or glutathione-transferase enzyme activities. However, Synercid has been shown to be an inhibitor of the CYP 3A4 isoenzyme. (See **Drug Interactions**.)

Fecal excretion constitutes the main elimination route for both parent drugs and their metabolites (75-77% of dose). Urinary excretion accounts for approximately 15% of the quinupristin and 19% of the dalfopristin dose. Preclinical data in rats have demonstrated that approximately 80% of the dose is excreted in the bile and suggest that in man, biliary excretion is probably the principal route for fecal elimination.

Special Populations

Elderly: The pharmacokinetics of quinupristin and dalfopristin are not modified in the elderly.

Gender: The pharmacokinetics of quinupristin and dalfopristin are not modified with gender.

Renal Insufficiency (Creatinine clearance 6-28 mL/min): The AUC of quinupristin and dalfopristin in combination with their major metabolites increased about 1.4- and 1.3- fold, respectively. (See **DOSAGE AND ADMINISTRATION**.)

In patients undergoing Continuous Ambulatory Peritoneal Dialysis, dialysis clearance for quinupristin, dalfopristin and their metabolites is negligible. The plasma AUC of unchanged quinupristin and dalfopristin increased about 1.2- and 1.3- fold, respectively. (See **DOSAGE AND ADMINISTRATION**.) The high molecular weight of both components of Synercid suggests that it is unlikely to be removed by hemodialysis.

Hepatic Insufficiency: In patients with hepatic cirrhosis, the terminal half-life of quinupristin and dalfopristin was not modified. However, the AUC of quinupristin and dalfopristin in combination

with their major metabolites increased about 2.8- and 1.5- fold, respectively.(See DOSAGE AND ADMINISTRATION and PRECAUTIONS.)

Obese: In obese patients, the Cmax and AUC of quinupristin increased about 1.3-fold and those of dalfopristin about 1.4-fold. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS.)

Pediatric Patients: The pharmacokinetics of **Synercid** in pediatric patients have not been studied.

Microbiology: The streptogramin components of **Synercid**, quinupristin and dalfopristin, individually possess bacteriostatic activity against Gram-positive bacteria, as do the principal components, PI and PIIA, of the naturally occurring streptogramin, pristinamycin. The main target of quinupristin and dalfopristin is the bacterial ribosome. When combined, quinupristin and dalfopristin, as **Synercid**, exert bactericidal activity by inhibiting early and late phases of bacterial protein synthesis and interact synergistically at the ribosomal site so that **Synercid**'s activity is much greater than that of the components individually. Therefore, the mode of action of streptogramins, e.g., **Synercid**, differs somewhat from that of the macrolides and lincosamides.

The high affinity of **Synercid** to bind to the ribosome contributes to its bactericidal activity which is uncharacteristic of the non-streptogramin members of the Macrolide-Lincosamide-Streptogramin (MLS) antibiotics. Consequently, **Synercid** has improved activity against pathogens resistant to macrolides and lincosamides. **Synercid** is also frequently active against pathogens resistant to β -lactam, glycopeptide, and quinolone antibiotics due to differences in chemical structure and mode of action.

A prolonged post-antibiotic effect (PAE) of **Synercid** was observed with *Staphylococcus aureus* (10 hours) and *Streptococcus pneumoniae* (9.1 hours) in the neutropenic mouse thigh abscess model, confirming *in vitro* data.

In vitro tests with *S. aureus*, including methicillin- and erythromycin-resistant strains, often show **Synercid** to act synergistically with some β -lactam agents, especially the cephalosporins. *In vitro* tests with some strains of vancomycin-resistant *E. faecium* show **Synercid** to act synergistically with glycopeptides.

Antagonism was generally not reported for any Gram-positive pathogens. *In vitro* tests with antibiotics active against *Pseudomonas aeruginosa* or *Enterobacteriaceae*, e.g. cefotaxime, ciprofloxacin, aztreonam, or gentamicin, did not show antagonism with **Synercid**.

Quinupristin and dalfopristin's metabolites also contribute to the antimicrobial activity of **Synercid** because their MICs range from comparable to severalfold lower than those of either quinupristin or dalfopristin. In addition, *in vitro* synergism of the major metabolites with the complementary parent compound has been demonstrated. (See Pharmacokinetics.)

Synercid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive microorganisms

Enterococcus faecium (including Van A {Vancomycin-resistant and Teicoplanin-resistant} and Van B {Vancomycin-resistant and Teicoplanin-susceptible} strains)
Staphylococcus aureus (including methicillin-resistant strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus pyogenes
Streptococcus pneumoniae (penicillin-susceptible strains)

The following *in vitro* data are available, **but their clinical significance is unknown.**

Synercid exhibits *in vitro* minimal inhibitory concentrations (MICs) of $\leq 1 \mu\text{g/mL}$ against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of Synercid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Corynebacterium jeikeium
Listeria monocytogenes
Staphylococcus capitis
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Staphylococcus simulans
Staphylococcus warneri
Streptococcus pneumoniae (penicillin-resistant strains)
Viridans group streptococci

Aerobic gram-negative microorganisms

Legionella pneumophila
Legionella spp
Moraxella catarrhalis
Neisseria gonorrhoeae (including β -lactamase-producing strains)
Neisseria meningitidis

Anaerobic microorganisms

Porphyromonas asaccharolytica

Atypical microorganisms

Chlamydia pneumoniae
Mycoplasma pneumoniae

SUSCEPTIBILITY TESTS

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of quinupristin/dalfopristin (30:70) powder (1). The MIC values should be interpreted according to the following criteria:

For testing rapidly growing aerobic microorganisms and *S. pneumoniae*:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1	Susceptible (S)
2	Moderately Susceptible (MS)
≥ 4	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Moderately Susceptible" indicates that the result should be considered equivocal, and if the infection cannot be treated with alternative, clinically feasible drugs, the test should be repeated. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control organisms to control the technical aspects of the laboratory procedures. Standard quinupristin/dalfopristin powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>Staphylococcus aureus</i> ATCC 29213	0.25 to 1
<i>Streptococcus pneumoniae</i> ATCC 49619*	0.25 to 1
<i>Enterococcus faecalis</i> ATCC 29212	2 to 8

* This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed (freeze thaw method) horse blood (1).

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations (2). This procedure uses paper disks impregnated with 15 µg quinupristin/dalfopristin (30:70) to test the susceptibility of microorganisms to Synercid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg quinupristin/dalfopristin disk should be interpreted according to the following criteria:

For testing rapidly growing aerobic microorganisms and *S. pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	Susceptible (S)
16-18	Moderately Susceptible (MS)
≤ 15	Resistant (R)

Interpretation should be stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for quinupristin/dalfopristin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control organisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-µg quinupristin/dalfopristin disk should provide the following zone diameters in these laboratory test quality control strains:

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>Staphylococcus aureus</i> ATCC 25923	23-29
<i>Streptococcus pneumoniae</i> ATCC 49619 ^a	19-24

^a This quality control range is applicable to only *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% whole sheep blood incubated in 5% CO₂.

INDICATIONS AND USAGE

Synercid is indicated in adults for the treatment of the following infections when caused by susceptible strains of the designated microorganisms, for which intravenous therapy is appropriate.

Synercid should be used in combination with appropriate anti-Gram-negative antibiotics if culture-proven or suspected pathogens are Gram-negative.

Complicated skin and skin structure infections caused by *Staphylococcus aureus* (including methicillin-resistant strains), *Staphylococcus epidermidis* (including methicillin-resistant strains), *Streptococcus agalactiae*, and *Streptococcus pyogenes*, including cases associated with concurrent bacteremia with these microorganisms.

Nosocomial pneumonia caused by *Staphylococcus aureus* (including methicillin-resistant strains) and *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia with these microorganisms.

Community-acquired pneumonia caused by culture-proven monomicrobial *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia.

Infections due to Vancomycin-resistant *Enterococcus faecium* (VREF), including cases associated with concurrent bacteremia.

Infections caused by *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), in patients failing other therapies, including cases associated with concurrent bacteremia.

Synercid was used successfully in a limited number of pediatric patients in non-comparative clinical studies.

Synercid can be used for treatment of the above indications in beta-lactam-, quinolone- or glycopeptide-allergic or -intolerant patients.

CONTRAINDICATIONS

Synercid is contraindicated in patients with known hypersensitivity to **Synercid** or with prior hypersensitivity to other streptogramins (e.g. pristinamycin or virginiamycin).

WARNINGS

Synercid infusion should not be administered as an intravenous bolus.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Synercid, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General: Following completion of the infusion, the vein should be flushed with 5% Dextrose solution to minimize venous irritation. It is recommended not to flush with saline or heparin immediately after Synercid administration.

If moderate to severe venous irritation occurs following peripheral administration of Synercid, consideration should be given to increasing the infusion volume to 500 or 750 mL, changing the infusion site, or infusing by a peripherally inserted central catheter (PICC) or a central venous catheter.

The safety and efficacy of an intravenous infusion duration other than 60 minutes have not been studied.

Episodes of arthralgia and myalgia, some severe, have been reported primarily in patients treated with a q8h regimen. In case severe or protracted arthralgia and myalgia occur, a switch to a q12h regimen may be considered.

Data from clinical trials of Synercid suggest that the incidence of adverse effects in patients with chronic liver insufficiency or cirrhosis was comparable to that in patients with normal hepatic function. Based on the pharmacokinetic parameters in patients with hepatic cirrhosis, a dosage reduction to 5 mg/kg of Synercid is recommended if the tolerability of Synercid at the dose of 7.5 mg/kg is not acceptable. (See **Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**.)

As with other antimicrobials, use of Synercid may result in overgrowth of non-susceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

Drug Interactions: *In vitro* drug interaction studies have demonstrated that only CYP 3A4 is significantly inhibited by Synercid. In *in vitro* studies, Synercid inhibited the CYP 3A4 metabolism of cyclosporin A, midazolam, nifedipine and terfenadine. Thus, it is reasonable to expect that the concomitant administration of Synercid and other drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in plasma levels of these drugs that could prolong their therapeutic effect and/or increase adverse reactions. Therefore, dosage adjustment of these agents may be necessary. Concomitant administration of a single dose of cyclosporin A and Synercid in healthy volunteers led to elevated plasma levels of cyclosporin A. Therefore, a dosage reduction of cyclosporin A based on monitoring of cyclosporin A levels may be necessary.

In vitro drug interaction studies have shown that Synercid does not significantly inhibit human CYP 1A2, 2A6, 2C9, 2C19, 2D6, or 2E1. Therefore, clinical interactions with drugs metabolized by these P450 isoenzymes are not expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been conducted with Synercid. Genetic toxicity studies were performed with Synercid, in bacterial *in vitro* and in both *in vivo* and *in vitro* mammalian tests. The tests used included the bacterial reverse mutation (Ames test), the CHO/HGPRT gene mutation test, the *in vitro* unscheduled DNA synthesis test in rat hepatocytes, the chromosome aberration test in CHO-K1 cells and the *in vivo* mouse micronucleus test in bone marrow. No evidence for *in vitro* mutagenic activity and no induction of DNA repair or *in vivo* clastogenic effect of Synercid, dalfopristin or quinupristin were detected with these tests. Synercid was negative in the *in vitro* chromosome aberration test in CHO-K1 cells. When tested individually, a positive response was observed with dalfopristin at highly cytotoxic concentrations. A negative response was observed with quinupristin.

No impairment of fertility or peri/post natal development was observed in rats.

Pregnancy:Teratogenic Effects: Pregnancy Category C: No teratogenic effect was evidenced in embryofetal toxicity studies performed in rats and mice with intravenous doses of Synercid up to 120 mg/kg/day (corresponding to approximately 5 times in rats and 2 times in mice the human daily recommended dose). Slight fetal immaturity was observed at 120 mg/kg/day and at 40 mg/kg/day in rats and mice, respectively. In rabbits, as expected from its antibacterial activity, the administration of Synercid from 2 to 120 mg/kg/day (corresponding to approximately 10 times lower to 5 times higher than the human daily recommended dose) produced gastrointestinal disturbances resulting in high maternal toxicity. This did not allow for the meaningful assessment of the relationship between Synercid and embryofetal development. However, no increased incidence of fetal malformations was noted.

There are, however, no adequate and well-controlled studies with Synercid in pregnant women. Because animal reproduction studies are not always predictive of the human response, Synercid should be used during pregnancy only if clearly needed.

Nursing mothers: In lactating rats, quinupristin was excreted in milk. It is not known whether Synercid is excreted in human breast milk. Consequently, Synercid should not be administered to a breast-feeding woman.

The following systemic adverse reactions were reported: arthralgia (9.5%), myalgia (7.3%), and asthenia (1.1%).

Adverse reactions reported with an incidence of less than 1% but greater than 0.1% included hyponatremia, anorexia, hypotension, back pain, cyclosporin level increased, tachycardia, jaundice, hepatitis and pharyngitis.

No cases of ototoxicity or Red Man Syndrome were reported in clinical trials with **Synercid**.

The clinical profile of **Synercid** suggests there is no nephrotoxic effect.

In these clinical trials, death was reported as possibly related to **Synercid** in 0.3% of patients.

Laboratory Changes: In the comparative clinical trials, increases in total and conjugated bilirubin greater than 5 times the ULN (Upper Limit of Normal) were reported in 0.9% and 3.1% of patients, respectively.

Other laboratory changes reported as clinically significant, irrespective of the relationship to **Synercid** administration, are listed below:

LABORATORY CHANGES	
Incidence greater than 1%	<i>increases</i> in eosinophils, blood urea nitrogen, gammaglutamyl transferase, lactate dehydrogenase, creatinine phosphokinase, AST, ALT, blood glucose, alkaline phosphatase, creatinine. <i>decreases</i> in hemoglobin, hematocrit. <i>increases and decreases</i> in potassium, platelets.

One case of severe thrombocytopenia was reported.

In addition in the non-comparative clinical trials, the discontinuation rate due to adverse laboratory reactions possibly or probably related to **Synercid** was 2.0%. Most patients discontinued because of liver function test abnormalities.

Decrease in white blood cells, carbon dioxide, neutrophils, and bicarbonate were reported, also with an incidence greater than 1%. One case of pancytopenia was reported.

OVERDOSAGE

No cases of overdose with **Synercid** have been reported. Patients who receive an overdose should be carefully observed and given supportive treatment. **Synercid** is not removed by peritoneal dialysis. (See **Pharmacokinetics**.) The high molecular weight of both components of **Synercid** suggests that it is unlikely to be removed by hemodialysis.

Pediatric use: The safety and efficacy of Synercid in pediatric patients was evaluated in a limited number of patients under emergency conditions at a dose of 7.5 mg/kg. (See INDICATIONS and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

The safety of Synercid was evaluated in 1099 patients enrolled in 5 comparative clinical trials (2 for Complicated skin and skin structure infections, 1 for Nosocomial pneumonia, and 2 for Community-acquired pneumonia). Additionally, 4 non-comparative clinical trials were conducted in 1199 patients who received Synercid for infections due to Gram-positive pathogens for which no other treatment option was appropriate. In this population, the patients were severely ill, with multiple background diseases, physiological impairments, and intolerant to other antibacterial therapies.

In the comparative clinical trials, the discontinuation rate due to adverse reactions possibly or probably related to Synercid was 6.1% for systemic reactions and 10.7% for local reactions, respectively. For the systemic adverse reactions, most patients discontinued due to rash (1%), nausea (0.8%), vomiting (0.5%), pruritus (0.5%), and pain (0.5%).

Adverse reactions possibly or probably related to Synercid administration are listed below:

ADVERSE REACTIONS	
Incidence equal to or greater than 1%	<p>Local adverse reactions: inflammation (42%), pain (40%), edema (17.3%), infusion site reaction (13.4%), thrombophlebitis (2.4%)</p> <p>Systemic adverse reactions: nausea (4.6%), diarrhea (2.7%), vomiting (2.7%) rash (2.5%), headache (1.6%), pruritus (1.5%), pain (1.5%).</p>

Additional adverse reactions that were possibly or probably related to Synercid with an incidence less than 1% but greater than 0.1% within each body system are listed below:

Body as a whole: abdominal pain, aggravation reaction, allergic reaction, cellulitis, chest pain, fever, infection;

Cardiovascular: palpitation, phlebitis;

Digestive: constipation, dyspepsia, oral moniliasis, pancreatitis, pseudomembranous enterocolitis, stomatitis;

Metabolic: gout, peripheral edema;

Musculoskeletal: arthralgia, myalgia, myasthenia;

Nervous: anxiety, confusion, dizziness, hypertonia, insomnia, leg cramps, paresthesia, vasodilatation;

Respiratory: dyspnea, pleural effusion, pneumonia;

Skin and appendages: maculopapular rash, sweating, urticaria;

Urogenital: hematuria, urinary tract infection, vaginitis;

In addition, in the non-comparative trials, the discontinuation rate due to systemic and local adverse reactions was 5.4% and 0.7%, respectively. Most patients discontinued because of arthralgia (2.3%) and myalgia (1.8%).

DOSAGE AND ADMINISTRATION

The recommended dose of **Synercid** in adults is 7.5 mg/kg of actual body weight administered by intravenous administration (See **WARNINGS**) in 5% Dextrose solution over a 60-minute period, q8 hours or q12 hours. An infusion pump may be used to control the rate of infusion.

INDICATIONS*	Dose (mg/kg)	Frequency	Recommended Treatment Duration (days)
Complicated skin and skin structure infections	7.5	q12h	7
Community-acquired pneumonia caused by monomicrobial <i>Streptococcus pneumoniae</i>	7.5	q12h	7
Nosocomial pneumonia	7.5	q8h	10
Infections caused by Vancomycin-resistant <i>Enterococcus faecium</i>	7.5	q8h	**
Infections caused by <i>Staphylococcus aureus</i> (including methicillin-susceptible and methicillin-resistant strains)	7.5	q8h	**

* including cases associated with concurrent bacteremia

**depends on site and severity of infection

Special Populations

Elderly: No dosage adjustment of **Synercid** is required for use in the elderly. (See **Pharmacokinetics**.)

Renal insufficiency: No dosage adjustment of **Synercid** is required for use in renally impaired patients and patients undergoing peritoneal dialysis. (See **Pharmacokinetics**.)

Hepatic insufficiency: Data from clinical trials of **Synercid** suggest that the incidence of adverse effects in patients with chronic liver insufficiency or cirrhosis was comparable to that in patients with normal hepatic function. However, based on the pharmacokinetic parameters in patients with hepatic cirrhosis, a dosage reduction to 5 mg/kg of **Synercid** is recommended if the tolerability of **Synercid** at the dose of 7.5 mg/kg is not acceptable. (See **Pharmacokinetics** and **PRECAUTIONS**.)

Obese Patients: No dosage adjustment of **Synercid** is required for use in obese patients. (See **Pharmacokinetics**.)

Pediatric Patients: Based on the experience in a limited number of pediatric patients in non-comparative trials, no dosage adjustment of **Synercid** is required. (See **PRECAUTIONS**.)

Preparation and administration of solution:

1. Reconstitute the single dose vial by slowly adding 5 mL of Dextrose 5% or Sterile Water for injection.
2. Gently swirl the vial by manual rotation without shaking to ensure dissolution of contents while limiting foam formation.

3. Allow the solution to sit for a few minutes until all the foam has disappeared. The resulting solution should be clear. Vials reconstituted in this manner will give a solution of 100 mg/mL.
CAUTION: FURTHER DILUTION REQUIRED BEFORE INFUSION.
4. According to the patient's weight, the **Synercid** solution should be added to 250 mL of 5% Dextrose solution. An infusion volume of 100 mL may be used for central line infusions.
5. The desired dose should be administered by intravenous infusion over 60 minutes.

NOTE: As for other parenteral drug products, **Synercid** should be inspected visually for particulate matter prior to administration.

Incompatibilities: DO NOT DILUTE WITH SALINE SOLUTIONS SINCE SYNERCID IS NOT COMPATIBLE WITH THESE AGENTS. **Synercid** should not be mixed with, or physically added to, other drugs since compatibility has not been established.

With intermittent infusion of **Synercid** and other drugs through a common intravenous line, the line should be flushed before and after **Synercid** administration with 5% Dextrose solution.

Stability and Storage: Before Reconstitution: The unopened vials should be stored in a refrigerator at 2 to 8°C (36 to 46°F).

Reconstituted and Infusions Solutions: Since **Synercid** contains no antibacterial preservative, it should be reconstituted under strict aseptic conditions (e.g. Laminar Air Flow Hood). The reconstituted solution should be diluted within 30 minutes. Vials are for single use. The storage time of the diluted solution should be as short as possible to minimize the risk of microbial contamination. Stability of the diluted solution prior to the infusion is established as 5 hours at room temperature or 54 hours if stored under refrigeration 2 to 8°C (36 to 46°F). The solution should not be frozen.

HOW SUPPLIED

Synercid is supplied as a sterile freeze-dried pyrogen-free preparation in single-dose 10 mL type I glass vials serrated with aluminum body with dark blue flip-off cap.

Each vial contains sufficient quinupristin/dalfopristin to deliver 500 mg for intravenous administration. NDC 0075-9051-25 in trays of 25 vials.

CLINICAL STUDIES

Non-comparative clinical trials were conducted in eight countries. **Synercid** was used for infections due to Gram-positive pathogens for which no other treatment option was appropriate because of *in vitro* resistance of the infecting organism to all available appropriate agents, or because of the patient's intolerance of, or failure on, all available appropriate agents.

The overall response rate, which represents a combination of the clinical success rate (cure plus improvement) and the bacteriologic success rate (eradicated plus presumed eradicated), for the clinically evaluable and bacteriologically evaluable populations, respectively, by indication are as follows:

Indications (non-comparative trials)	Clinically Evaluable Population	Bacteriologically Evaluable Population
All Patients	72.2% (312/432)	68.0% (230/338)
Intra-Abdominal Infections	65.9% (91/138)	61.6% (69/112)
Bacteremia of Unknown Origin	70.4% (57/81)	64.6% (42/65)
Central Catheter-Related Bacteremia	82.9% (34/41)	78.1% (25/32)
Skin and Skin Structure Infection	74.5% (38/51)	71.1% (27/38)
Urinary Tract Infection	84.8% (39/46)	85.3% (29/34)
Bone and Joint Infection	81.1% (30/37)	80.8% (21/26)
Respiratory Tract Infections	76.9% (10/13)	66.7% (6/9)

Indications	Clinically Evaluable Population	Bacteriologically Evaluable Population
All Vancomycin-resistant <i>Enterococcus faecium</i> infections	69.8% (250/358)	65.5% (186/284)

Indications	Clinically Evaluable Population	Bacteriologically Evaluable Population
All <i>Staphylococcus aureus</i> Infections (including methicillin-susceptible and methicillin-resistant strains)	85.3% (29/34)	81.8% (18/22)

In order to interpret the breakpoints, clinical and bacteriologic patient outcomes versus MICs are given below:

Correlation of Satisfactory Patient Outcomes and Synercid MICs of Baseline Pathogens^a from Non-Comparative trials^b (Clinically and Bacteriologically Evaluable Population) (N/Total N (%))

	Clinical		Bacteriological	
	Success ^c	Failure	Eradication ^d	Persistence ^e
≤1 µg/mL	123/167 (73.7)	44/167 (26.3)	121/167 (72.5)	46/167 (27.5)
≤2 µg/mL	131/180 (72.8)	49/180 (27.2)	129/180 (71.7)	51/180 (28.3)
2 µg/mL	8/13 (61.5)	5/13 (38.5)	8/13 (61.5)	5/13 (38.5)

^a Includes vancomycin-resistant *E. faecium*, methicillin-sensitive and -resistant *S. aureus*, and other pathogens.

^b Patients who received Synercid for infections due to Gram-positive pathogens for which no other treatment option was appropriate.

^c Cure or improvement of clinical signs and symptoms.

^d Eradication or presumed eradication of baseline pathogen.

^e Persistence or presumed persistence of baseline pathogen.

At MICs of ≤ 1 or ≤ 2 µg/mL the satisfactory clinical and bacteriological response rates were comparable, i.e., 72 to 74%. At MICs of 2 µg/mL, the correlation was 62% (8/13). At MICs of ≥ 4 µg/mL the correlation was 75% (3/4). However, the number of observations was very small; consequently, results must be interpreted with caution.

Correlation of Satisfactory Patient Outcomes and Synercid MICs of Baseline Pathogens from Comparative trials^a (Clinically and Bacteriologically Evaluable Population) (N/Total N (%))

	Clinical		Bacteriological	
	Success ^b	Failure	Eradication ^c	Persistence ^d
≤1 µg/mL	192/275 (69.8) ^e	83/275 (30.2)	199/275 (72.4)	76/275 (27.6)
≤2 µg/mL	201/286 (70.3)	85/286 (29.7)	208/286 (72.7)	78/286 (27.3)
2 µg/mL	9/11 (81.8)	2/11 (18.2)	9/11 (81.8)	2/11 (18.2)

^a Nosocomial pneumonia, complicated skin and skin structure infections, and community-acquired pneumonia.

^b Cure or improvement of clinical signs and symptoms.

^c Eradication or presumed eradication of baseline pathogen.

^d Persistence or presumed persistence of baseline pathogen.

^e Pathogens assessed include staphylococci (including methicillin-resistant strains), streptococci, enterococci, and *M. catarrhalis*.

At MICs of ≤ 1 or ≤ 2 µg/mL the satisfactory clinical and bacteriological response rates for comparative studies were comparable, i.e., 70 to 74%. At MICs ≥ 4 µg/mL the correlation was 33% (3/9) to 22% (2/9), respectively. However, the number of observations was very small; consequently, results must be interpreted with caution.

Caution: Federal law prohibits dispensing without a prescription.

Keep out of the reach of children.

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United States Patent [19]

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[11] Patent Number: 4,668,669

[45] Date of Patent: May 26, 1987

[54] PRISTINAMYCIN II_B DERIVATIVES AND COMPOSITIONS CONTAINING THEM

[75] Inventors: Jean-Claude Barriere, Massy; Claude Cotrel, Paris; Jean-Marc Paris, Vaires sur Marne, all of France

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[21] Appl. No.: 817,548

[22] Filed: Jan. 10, 1986

[30] Foreign Application Priority Data

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[51] Int. Cl.⁴ A61K 31/42; C07D 498/14;

C07K 5/12

[52] U.S. Cl. 514/183; 530/317;

540/455

[58] Field of Search 260/239.3 T; 514/183; 540/455; 530/317

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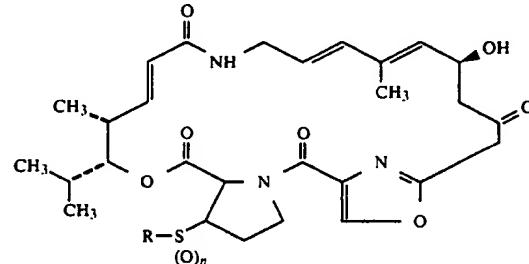
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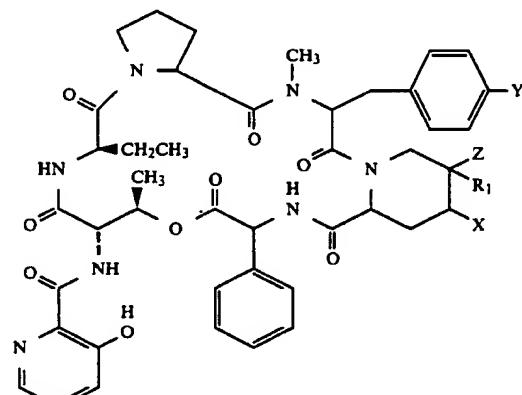
Primary Examiner—Robert T. Bond
Attorney, Agent, or Firm—Stevens, Davis, Miller & Mosher

[57] ABSTRACT

Pristinamycin II_B derivatives of formula:



in which R denotes a nitrogen-containing 4 to 7-membered heterocyclic ring optionally substituted by alkyl; or alkyl (2 to 4 C) substituted by 1 or 2 phenyl, cycloalkylamino or N-alkyl-N-cycloalkylamino (3 to 6 ring atoms), alkylamino, dialkylamino or dialkylcarbamoyloxy radicals (the dialkylamino moieties of these 2 latter radicals being capable of forming a 4 to 7-membered cyclic ring optionally substituted by alkyl) or substituted by 1 or 2 nitrogen-containing 4 to 7 membered heterocyclic rings, optionally substituted by alkyl, at least one of the above substituents being a nitrogen-containing substituent capable of forming salts and n is 1 or 2, all the alkyls being linear or branched and containing (unless stated otherwise) 1 to 10 carbon atoms, their isomers, their salts and their preparation. These compounds, optionally in combination with known synergistins or synergistins of formula:



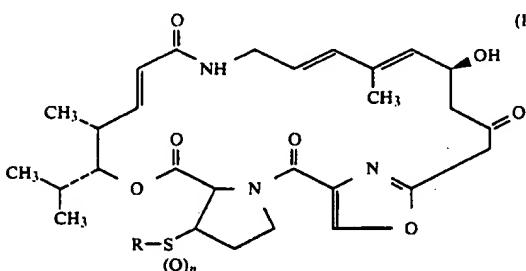
are useful as antimicrobial agents.

10 Claims, No Drawings

PRISTINAMYCIN II_B DERIVATIVES AND COMPOSITIONS CONTAINING THEM

This invention relates to pristinamycin II_B derivatives their preparation, and compositions containing them.

The present invention provides new pristinamycin II_B derivatives, of the formula:



and their acid addition salts, in which R denotes: either a nitrogen-containing 4 to 7-membered heterocyclic ring radical, which may contain 1 or more other hetero atoms chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl; or alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, alkylamino, dialkylamino and dialkylcarbamoyloxy, the alkyl parts of these 2 latter radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, a saturated or unsaturated 4 to 7-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl, or alkyl of 2 to 4 carbon atoms substituted by one or more nitrogen-containing, 4 to 7-membered heterocyclic rings which may contain 1 or 2 other hetero atoms chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl, these heterocyclic rings being linked to the alkyl by a carbon atom of the ring, at least one of the substituents carried by the said alkyl chain being a nitrogen-containing substituent capable of forming salts, and n is 1 or 2. The alkyl radicals and moieties referred to above are linear or branched and, unless mentioned otherwise, contain 1 to 10 carbon atoms.

The products of formula (I) have isomeric forms and their isomers and their mixtures are included within the scope of the present invention.

When R denotes a heterocyclic radical, this radical can be, for example: 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidyl or 3- or 4-azepinyl.

When R denotes an alkyl radical substituted by a heterocyclic ring radical, the heterocyclic ring radical can be chosen, for example, from the radicals listed above or the 2-azetidinyl, 2-pyrrolidinyl, 2-piperidyl, 2-azepinyl, piperazinyl, 4-alkylpiperazinyl, quinolyl, isoquinolyl or imidazolyl radicals.

When R contains a dialkylamino or dialkylcarbamoyloxy radical in which the alkyl moieties form a heterocyclic ring with the nitrogen atom to which they are attached, this ring can be chosen, for example, from: 1-azetidinyl, 1-pyrrolidinyl, piperidino, 1-azepinyl, morpholino, thiomorpholino in the form of sulphoxide or

sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-1-homopiperazinyl, or 1-imidazolyl.

The following compounds of general formula (I) can be mentioned, in particular, by way of example:

- 5 26-(3-azetidinyl)sulphinylpirstinamycin II_B
- 26-(1-methyl-3-azetidinyl)sulphinylpirstinamycin II_B
- 26-(1-ethyl-3-azetidinyl)sulphinylpirstinamycin II_B
- 26-(1-isopropyl-3-azetidinyl)sulphinylpirstinamycin II_B
- 26-(3-pyrrolidinyl)sulphinylpirstinamycin II_B
- 26-(1-methyl-3-pyrrolidinyl)sulphinylpirstinamycin II_B
- 26-(1-ethyl-3-pyrrolidinyl)sulphinylpirstinamycin II_B
- 26-(1-isopropyl-3-pyrrolidinyl)sulphinylpirstinamycin II_B
- 26-(3-piperidyl)sulphinylpirstinamycin II_B
- 26-(1-methyl-3-piperidyl)sulphinylpirstinamycin II_B
- 26-(1-ethyl-3-piperidyl)sulphinylpirstinamycin II_B
- 26-(4-piperidyl)sulphinylpirstinamycin II_B
- 26-(1-methyl-4-piperidyl)sulphinylpirstinamycin II_B
- 26-(1-ethyl-4-piperidyl)sulphinylpirstinamycin II_B
- 20 26-(3-azepinyl)sulphinylpirstinamycin II_B
- 26-(4-azepinyl)sulphinylpirstinamycin II_B
- 26-(2-cyclopropylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-cyclobutylaminoethyl)sulphinylpirstinamycin II_B
- 25 26-(2-cyclopentylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-cyclohexylaminoethyl)sulphinylpirstinamycin II_B
- 26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphinylpirstinamycin II_B
- 30 26-(2-methylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-ethylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-propylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-isopropylaminoethyl)sulphinylpirstinamycin II_B
- 35 26-(2-butylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-isobutylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-n-decylaminoethyl)sulphinylpirstinamycin II_B
- 26-(dimethylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-diethylaminoethyl)sulphinylpirstinamycin II_B
- 40 26-(2-dipropylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-diisopropylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-dibutylaminoethyl)sulphinylpirstinamycin II_B
- 26-(2-diisobutylaminoethyl)sulphinylpirstinamycin II_B
- 45 26-(N-ethyl-N-methyl-2-aminoethyl)sulphinylpirstinamycin II_B
- 26-[2-(1-azetidinyl)ethyl]sulphinylpirstinamycin II_B
- 26-[2-(1-pyrrolidinyl)ethyl]sulphinylpirstinamycin II_B
- 26-(2-piperidinoethyl)sulphinylpirstinamycin II_B
- 50 26-[2-(1-azepinyl)ethyl]sulphinylpirstinamycin II_B
- 26-(2-morpholinoethyl)sulphinylpirstinamycin II_B
- 26-[2-(1-piperazinyl)ethyl]sulphinylpirstinamycin II_B
- 26-[2-(4-methyl-1-piperazinyl)ethyl]sulphinylpirstinamycin II_B
- 26-[2-(4-methyl-1-homopiperazinyl)ethyl]sulphinylpirstinamycin II_B
- 26-[2-(1-imidazolyl)ethyl]sulphinylpirstinamycin II_B
- 26-(2-dimethylaminocarbamoyloxyethyl)sulphinylpirstinamycin II_B
- 26-(2-diethylaminocarbamoyloxyethyl)sulphinylpirstinamycin II_B
- 26-(2-diisopropylaminocarbamoyloxyethyl)sulphinylpirstinamycin II_B

26-[2-(4-methyl-1-piperazinyl)carbamoyloxyethyl]sulphinylpstinamycin II_B
 26-[2-(2-azetidinyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(3-azetidinyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(2-pyrrolidinyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(3-pyrrolidinyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(2-piperidyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(3-piperidyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(4-piperidyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(2-azepinyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(3-azepinyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(4-azepinyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(3-quinolyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(4-quinolyl)ethyl]sulphinylpstinamycin II_B
 26-[2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]sulphinylpstinamycin II_B
 26-82-(1-isoquinolyl)ethyl]sulphinylpstinamycin II_B
 26-(2-imidazolylethyl)sulphinylpstinamycin II_B
 26-(2-cyclopropylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-cyclobutylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-cyclopentylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(cyclohexylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-[2-(N-cyclohexyl-N-methyl-amino)-1-methylethyl]sulphinylpstinamycin II_B
 26-(2-methylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-ethylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(1-methyl-2-propylaminoethyl)sulphinylpstinamycin II_B
 26-(2-isopropylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-butylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-isobutylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(1-methyl-2-n-decylaminoethyl)sulphinylpstinamycin II_B
 26-(2-dimethylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-diethylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-dipropylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-diisopropylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-dibutylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-(2-diisobutylamino-1-methylethyl)sulphinylpstinamycin II_B
 26-[2-(N-ethyl-N-methyl-amino)-1-methylethyl]sulphinylpstinamycin II_B
 26-[2-(1-azetidinyl)-1-methylethyl]sulphinylpstinamycin II_B
 26-[1-methyl-2-(1-pyrrolidinyl)ethyl]sulphinylpstinamycin II_B
 26-(1-methyl-2-piperidinoethyl)sulphinylpstinamycin II_B

26-[2-(1-azepinyl)-1-methylethyl]sulphinylpristinamycin II_B
 26-(1-methyl-2-morpholinoethyl)sulphinylpristinamycin II_B
 5 26-[1-methyl-2-(1-piperazinyl)ethyl]sulphinylpristinamycin II_B
 26-[2-(4-methyl-1-piperazinyl)-1-methylethyl]sulphinylpristinamycin II_B
 10 26-[2-(4-methyl-1-homopiperazinyl)-1-methylethyl]sulphinylpristinamycin II_B
 26-[2-(1-imidazolyl)-1-methylethyl]sulphinylpristinamycin II_B 26-(2-dimethylaminocarbamoyloxy-1-methylethyl)sulphinylpristinamycin II_B
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 25 26-[2-(3-azetidinyl)-1-methylethyl]sulphinylpristinamycin II_B
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 26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphinylpristinamycin II_B
 30 26-[1-methyl-2-(2-piperidyl)ethyl]sulphinylpristinamycin II_B
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 26-[1-methyl-2-(4-piperidyl)ethyl]sulphinylpristinamycin II_B
 35 26-[2-(2-azepinyl)-1-methylethyl]sulphinylpristinamycin II_B
 26-[2-(3-azepinyl)-1-methylethyl]sulphinylpristinamycin II_B
 26-[2-(4-azepinyl)-1-methylethyl]sulphinylpristinamycin II_B
 40 26-[1-methyl-2-(3-quinolyl)ethyl]sulphinylpristinamycin II_B
 26-[1-methyl-2-(4-quinolyl)ethyl]sulphinylpristinamycin II_B
 45 26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]sulphinylpristinamycin II_B
 26-[2-(1-isoquinolyl)-1-methylethyl]sulphinylpristinamycin II_B
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 50 II_B
 26-(2-cyclopropylamino-2-methylethyl)sulphinylpristinamycin II_B
 26-(2-cyclobutylamino-2-methylethyl)sulphinylpristinamycin II_B
 55 26-(2-cyclopentylamino-2-methylethyl)sulphinylpristinamycin II_B
 26-(2-cyclohexylamino-2-methylethyl)sulphinylpristinamycin II_B
 26-[2-(N-cyclohexyl-N-methylamino)-2-methylethyl]-sulphinylpristinamycin II_B
 60 26-(2-methylamino-2-methylethyl)sulphinylpristinamycin II_B
 26-(2-ethylamino-2-methylethyl)sulphinylpristinamycin II_B
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26-(2-methyl-2-propylaminoethyl)sulphinylpristinamycin II_B
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 26-(2-dimethylamino-2-methylethyl)sulphinylpristinamycin II_B
 26-(2-diethylamino-2-methylethyl)sulphinylpristinamycin II_B
 26-(2-dipropylamino-2-methylethyl)sulphinylpristinamycin II_B
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 26-[2-(N-ethyl-N-methyl-amino)-2-methylethyl]sulphinylpristinamycin II_B
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 26-(2-methyl-2-piperidinoethyl)sulphinylpristinamycin II_B
 26-[2-(1-azepinyl)-2-methylethyl]sulphinylpristinamycin II_B
 26-(2-methyl-2-morpholinoethyl)sulphinylpristinamycin II_B
 26-[2-methyl-2-(1-piperazinyl)ethyl]sulphinylpristinamycin II_B
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26-[2-(2-azepinyl)-2-methylethyl]sulphinylpristinamycin II_B
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 26-(2-dimethylamino-3-phenylpropyl)sulphinylpristinamycin II_B
 26-(2-dimethylaminobutyl)sulphinylpristinamycin II_B
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 26-(1-ethyl-3-azetidinyl)sulphonylpristinamycin II_B
 26-(1-isopropyl-3-azetidinyl)sulphonylpristinamycin II_B
 26-(3-pyrrolidinyl)sulphonylpristinamycin II_B
 25 26-(1-methyl-3-pyrrolidinyl)sulphonylpristinamycin II_B
 26-(1-ethyl-3-pyrrolidinyl)sulphonylpristinamycin II_B
 26-(1-isopropyl-3-pyrrolidinyl)sulphonylpristinamycin II_B
 26-(3-piperidyl)sulphonylpristinamycin II_B
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 26-(1-ethyl-4-piperidyl)sulphonylpristinamycin II_B
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 26-(4-azepinyl)sulphonylpristinamycin II_B
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 60 26-(2-dibutylaminooethyl)sulphonylpristinamycin II_B
 26-(2-diisobutylaminooethyl)sulphonylpristinamycin II_B
 26-(N-ethyl-N-methyl-2-aminoethyl)sulphonylpristinamycin II_B

26-[2-(1-azetidinyl)ethyl]sulphonylpristinamycin II_B
 26-[2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B
 26-(2-piperidinoethyl)sulphonylpristinamycin II_B
 26-[2-(1-azepinyl)ethyl]sulphonylpristinamycin II_B
 26-(2-morpholinoethyl)sulphonylpristinamycin II_B
 26-[2-(1-piperazinyl)ethyl]sulphonylpristinamycin II_B
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 26-[2-(4-methyl-1-homopiperazinyl)ethyl]sulphonylpristinamycin II_B
 26-[2-(1-imidazolyl)ethyl]sulphonylpristinamycin II_B
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 26-[2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B
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 26-[2-(4-piperidyl)ethyl]sulphonylpristinamycin II_B
 26-[2-(2-azepinyl)ethyl]sulphonylpristinamycin II_B
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 26-[2-(4-azepinyl)ethyl]sulphonylpristinamycin II_B
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 26-(2-cyclobutylamino-1-methylethyl)sulphonylpristinamycin II_B
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 26-(2-cyclohexylamino-1-methylethyl)sulphonylpristinamycin II_B
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26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin II_B
 26-(2-dipropylamino-1-methylethyl)sulphonylpristinamycin II_B
 5 26-(2-diisopropylamino-1-methylethyl)sulphonylpristinamycin II_B
 26-(2-dibutylamino-1-methylethyl)sulphonylpristinamycin II_B
 26-(2-diisobutylamino-1-methylethyl)sulphonylpristinamycin II_B
 10 26-[2-(N-ethyl-N-methyl-amino)-1-methylethyl][sulphonylpristinamycin II_B
 26-[2-81-(azetidinyl)-1-methylethyl]sulphonylpristinamycin II_B
 15 26-[1-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B
 26-(1-methyl-2-piperidinoethyl)sulphonylpristinamycin II_B
 26-[2-(1-azepinyl)-1-methylethyl]sulphonylpristinamycin II_B
 20 26-[1-methyl-2-(1-piperazinyl)ethyl]sulphonylpristinamycin II_B
 26-(1-methyl-2-morpholinoethyl)sulphonylpristinamycin II_B
 26-[1-methyl-2-(1-piperazinyl)ethyl]sulphonylpristinamycin II_B
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 26-[2-(4-methyl-1-homopiperazinyl)-1-methylethyl]sulphonylpristinamycin II_B
 26-[2-(1-imidazolyl)-1-methylethyl]sulphonylpristinamycin II_B
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 26-(2-diethylaminocarbamoyloxy-1-methylethyl)-sulphonylpristinamycin II_B
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 26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-1-methylethyl]sulphonylpristinamycin II_B
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 26-[2-(3-azetidinyl)-1-methylethyl]sulphonylpristinamycin II_B
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 45 26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B
 26-[1-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin II_B
 26-[1-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin II_B
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 26-[1-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin II_B
 60 26-[1-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin II_B
 26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin II_B

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26-(2-ethylamino-2-methylethyl)sulphonylpristinamycin II_B

26-(2-methyl-2-propylaminoethyl)sulphonylpristinamycin II_B

26-(2-isopropylamino-2-methylethyl)sulphonylpristinamycin II_B

26-(2-butylamino-2-methylethyl)sulphonylpristinamycin II_B

26-(2-isobutylamino-2-methylethyl)sulphonylpristinamycin II_B

26-(2-methyl-2-n-decylaminoethyl)sulphonylpristinamycin II_B

26-(2-dimethylamino-2-methylethyl)sulphonylpristinamycin II_B

26-(2-diethylamino-2-methylethyl)sulphonylpristinamycin II_B

26-(2-dipropylamino-2-methylethyl)sulphonylpristinamycin II_B

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26-(2-dibutylamino-2-methylethyl)sulphonylpristinamycin II_B

26-[2-(N-ethyl-N-methyl-amino)-2-methylethyl]sulphonylpristinamycin II_B

26-[2-(1-azetidinyl)-2-methylethyl]sulphonylpristinamycin II_B

26-[2-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B

26-(2-methyl-2-piperidinoethyl)sulphonylpristinamycin II_B

26-[2-(1-azepinyl)-2-methylethyl]sulphonylpristinamycin II_B

26-(2-methyl-2-morpholinoethyl)sulphonylpristinamycin II_B

26-[2-methyl-2-(1-piperazinyl)ethyl]sulphonylpristinamycin II_B

26-[2-(4-methyl-1-piperazinyl)-2-methylethyl]sulphonylpristinamycin II_B

26-[2-(4-methyl-1-homopiperazinyl)-2-methylethyl]sulphonylpristinamycin II_B

26-[2-(1-imidazolyl)-2-methylethyl]sulphonylpristinamycin II_B

26-(2-dimethylaminocarbamoyloxy-2-methylethyl)sulphonylpristinamycin II_B

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26-(2-diisopropylaminocarbamoyloxy-2-methylethyl)sulphonylpristinamycin II_B

26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-2-methylethyl]sulphonylpristinamycin II_B

5 26-[2-(2-azetidinyl)-2-methylethyl]sulphonylpristinamycin II_B

26-[2-(3-azetidinyl)-2-methylethyl]sulphonylpristinamycin II_B

10 26-[2-methyl-2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B

26-[2-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin II_B

26-[2-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin II_B

15 26-[2-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin II_B

26-[2-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin II_B

20 26-[2-(2-azepinyl)-2-methylethyl]sulphonylpristinamycin II_B

26-[2-(3-azepinyl)-2-methylethyl]sulphonylpristinamycin II_B

26-[2-(4-azepinyl)-2-methylethyl]sulphonylpristinamycin II_B

25 26-[2-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin II_B

26-[2-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin II_B

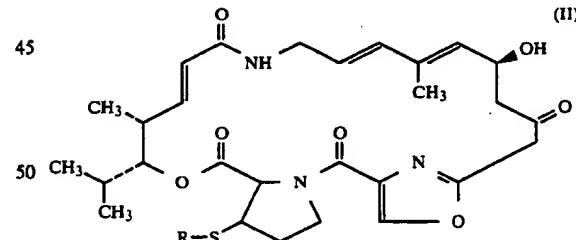
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26-[2-(1-isoquinolyl)-2-methylethyl]sulphonylpristinamycin II_B

35 26-(2-dimethylamino-3-phenylpropyl)sulphonylpristinamycin II_B

26-(2-dimethylaminobutyl)sulphonylpristinamycin II_B

According to the invention, the products of general formula (I) can be prepared by oxidation of a derivative of pristinamycin II_B, of its salt or of a protected derivative, of general formula:



55 in which R is defined as above, it being understood that in the cases where R contains a sulphur-containing hetero cyclic ring, the sulphur atom can be in the form of a sulphide, sulphoxide or sulphone.

The reaction is generally carried out by means of an oxidizing agent, optionally prepared in situ, in an aqueous medium or in an organic solvent, preferably a chlorinated solvent (methylene chloride, 1,2-dichloroethane or chloroform, for example) or an alcohol (methanol or tert-butanol, for example) or a mixture of these solvents.

65 Optionally the operation can be carried out under nitrogen.

Among the oxidizing agents which are suitable for preparing a product of general formula (I) in which $n=1$, it is possible to mention organic peracids: percarboxylic or persulphonic acids (for example peracetic, pertrifluoroacetic, performic, perbenzoic, m-chloroperbenzoic, p-nitroperbenzoic, permaleic, monoperphthalic, percamphoric or p-toluenepersulphonic acids) or inorganic peracids (for example periodic or persulphuric acid).

When the intention is to prepare a product of general formula (I) in which $n=2$, the operation is advantageously carried out in the presence of selenium dioxide and hydrogen peroxide, using the salt of the product of general formula (II), or in the presence of a peracid such as those referred to above, especially pertrifluoroacetic acid, or m-chloroperbenzoic acid.

When the derivative of pristinamycin II_B of general formula (II) is used in the form of a salt, use is made of the salts formed with organic or inorganic acids, preferably with trifluoroacetic, tartaric, acetic, benzoic, or hydrochloric acids.

When the product of general formula (II) is used in the form of a salt or of a protected derivative, the reaction is advantageously carried out at a temperature between -40° and 50° C.

When it is intended to prepare a product of general formula (I) in which $n=1$, it is also advantageous to operate by starting from the derivative of pristinamycin II_B of general formula (II) in the presence of an alkali metal bicarbonate (for example sodium bicarbonate) at a temperature between -60° and -40° C.

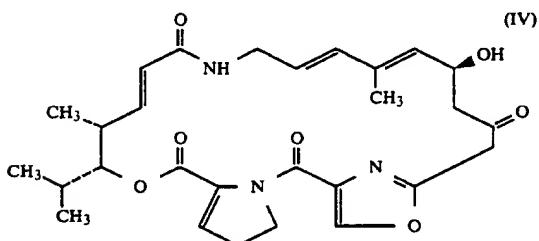
When R contains an alkylamino or cycloalkylamino substituent, it is also possible to utilize a protected derivative of the product of general formula (II). The latter can be protected by any amine-protective group whose introduction and removal do not affect the remainder of the molecule; use is advantageously made of the trifluoroacetyl group which can be removed after the reaction by treatment with an alkali metal bicarbonate (sodium or potassium bicarbonate) in an aqueous solution.

The products of general formula (II) can be prepared by the reaction of a product of general formula:



(III)

in which R is defined as above, with the product of formula:



that is to say pristinamycin II_A.

The reaction is usually carried out in an organic solvent such as an alcohol such as methanol or ethanol, or a chlorinated solvent such as methylene chloride, 1,2-dichloroethane or chloroform, or in a mixture of these solvents (for example methylene chloride/methanol) at a temperature between -30° and 50° C.

Occasionally it may be advantageous to operate in the presence of a tertiary amine, for example triethylamine,

or of an ethanolamine (for example dimethylethanamine).

A person skilled in the art will understand that, when R denotes a radical containing a secondary amine group capable of interfering with the reaction, this group will need to be protected beforehand, before the product of general formula (III) is reacted with the product of formula (IV). Any usual means which enables a secondary amine function to be blocked in the form of a labile radical can be used for this purpose. It is especially advantageous to use the trifluoroacetyl radical as a blocking radical which can be removed as described above. In such a case, however, it is not absolutely essential to remove the protective radical, and the protected derivative can be used directly in the oxidation reaction.

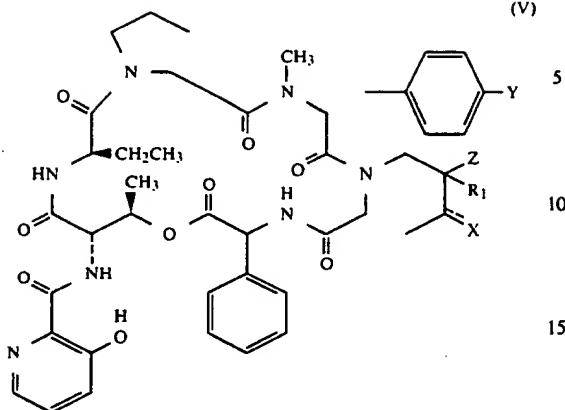
According to the invention, the products of general formula (I) in which n is equal to 2 can also be prepared by the oxidation of a product of general formula (I) in which n is equal to 1.

The reaction is carried out under conditions which are similar to the conditions described above for preparing a product of general formula (I) in which n=2 starting from a pristinamycin II_B derivative of general formula (II).

The new products of general formula (I) can be purified by known methods, for example by crystallization, chromatography or successive extractions in an acidic or basic medium. For the person skilled in the art who is aware of the sensitivity of synergistins in an alkaline medium, a "basic medium" is understood to mean a medium which is just alkaline enough to liberate the parent substance from its salt of addition with an acid, that is to say a medium whose pH does not exceed 8.

It is well known that the synergistins obtained by fermentation constitute products which are greatly sought after by medical practitioners for the treatment of many complaints due to Gram-positive bacteria (of the Staphylococci, Streptococci, pneumococci or enterococci type) and Gram-negative bacteria (of the Haemophilus, gonococci, meningococci type). However, these products have the disadvantage of being insoluble in an aqueous medium and consequently can be administered only by oral route, generally in the form of gelatine capsules, coated pills or tablets. In view of this insolubility, it has hitherto been impossible to use the known synergistins when the patient is unable to swallow; this is the case, in particular, in paediatrics and in reanimation, while the activity spectrum of these products would render them a valuable indication in many circumstances, for example in cases of comatose septicaemias.

The new products according to the invention have the considerable advantage of being capable of being dissolved in water, usually in the form of salts, in usable therapeutic doses, and of enhancing, via a synergism phenomenon, the antibacterial action of pristinamycin I_A, virginiamycin S or of derivatives of soluble synergistins of general formula:



in which Y denotes a hydrogen atom or a dimethyl- 20
amino radical and

(1) either —— denotes a single bond, Z and R₁ denote a
hydrogen atom and X denotes a radical of general
formula:



in which:

either R₂ denotes a hydrogen atom and R₃ denotes a
hydroxy or alkyl radical optionally substituted by a
carboxy, alkoxycarbonyl, hydroxy, alkylamino or
dialkylamino radical whose alkyl radicals can 35
form, with the nitrogen atom to which they are
attached, a 4 to 7-membered hetero-cyclic ring
chosen from azetidinyl, pyrrolidinyl, piperidinyl,
piperazinyl, N-alkylpiperazinyl or azepinyl rings,
or R₃ denotes a cycloalkyl radical containing 3 to 7 40
carbon atoms or a saturated 4 to 7-membered hetero-
ocyclic ring chosen from the azetidine, pyrrolidine,
piperidine and azepine rings, these heterocyclic
rings being optionally capable of being substituted
by an alkyl radical on the nitrogen atom, 45
or R₂ denotes a formyl or alkylcarbonyl radical and
R₃ denotes an alkyl radical substituted by a car-
boxy, alkylamino or dialkylamino radical whose
alkyl radicals can form, with the nitrogen atom to
which they are attached a 4 to 7-membered hetero- 50
cyclic ring chosen from azetidinyl, pyrrolidinyl,
piperidinyl, piperazinyl, N-alkylpiperazinyl or
azepinyl ring, or R₃ denotes a 4 to 7-membered
heterocyclic ring chosen from the azetidine, pyr- 55
rolidine, piperidine and azepine rings, these hetero-
cyclic rings being capable of being substituted by
an alkyl radical on the nitrogen atom,

or R₂ and R₃, which are identical or different, denote
an alkyl radical optionally substituted by a car-
boxy, alkoxycarbonyl, hydroxy, alkylamino or
dialkylamino radical whose alkyl radicals option- 60
ally form, with the nitrogen atom to which they are
attached, a 4 to 7-membered heterocyclic ring
chosen from azetidinyl, pyrrolidinyl, piperidinyl,
piperazinyl, N-alkylpiperazinyl or azepinyl.

or R₂ and R₃ form, together with the nitrogen atom to
which they are attached, a 4 to 7-membered hetero-
cyclic ring chosen from the azetidine, pyrrolidine,

piperidine, morpholine and piperazine rings, op-
tionally substituted by an alkyl radical,
(2) or —— denotes a double bond, X denotes an oxygen
atom and Z denotes a radical of general formula:



defined as follows:

(a) either R₁ and R₅ each denote a hydrogen atom and
R₄ denotes a 3-pyrrolidinylthio or 3- or 4-piper-
dylthio radical (these radicals being optionally
substituted by an alkyl radical) or R₄ denotes an
alkylthio radical substituted by one or two hydrox-
ysulphonyl, alkylamino, or dialkylamino (option-
ally substituted by a mercapto or dialkylamino
radical) radicals, or by one or two rings chosen
from piperazino (optionally substituted by an alkyl
or mercaptoalkyl radical) morpholino, thiomor-
pholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-
piperidyl and 2- or 3-pyrrolidinyl radicals (the lat-
ter two rings being optionally substituted by an
alkyl radical on the nitrogen atom),

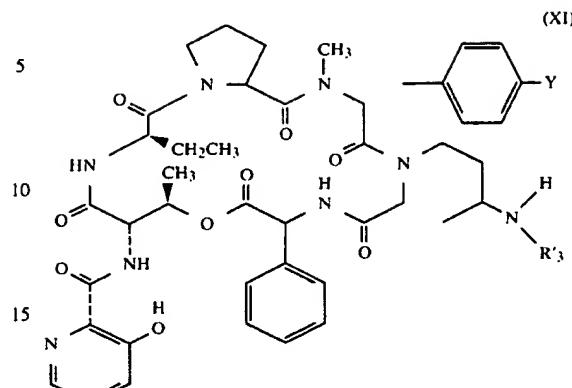
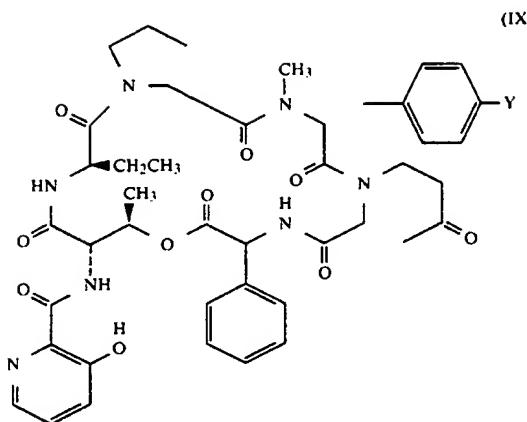
(b) or R₁ and R₅ together form a valency bond and
R₄ denotes a 3-pyrrolidinylamino, 3- or 4-
piperidylamino, 3-pyrrolidinyloxy, 3- or 4-
piperidyloxy, 3-pyrrolidinylthio or 3- or 4-piper-
dylthio radical (these radicals being optionally
substituted by an alkyl radical on the nitrogen atom
in the ring), or R₄ denotes an alkylamino, alkyl-
oxy or alkylthio radical substituted by one or two hydrox-
ysulphonyl, alkylamino, dialkylamino (option-
ally substituted by a dialkylamino radical), trialk-
ylammonio or 4- or 5-imidazolyl radicals or by one
or two rings chosen from piperazino (optionally
substituted by an alkyl or mercapto alkyl radical),
morpholino, thiomorpholino, piperidino, 1-pyr-
rolidinyl, 2-, 3- or 4-piperidinyl and 2- or 3-pyr-
rolidinyl radical (the last two rings being optionally
substituted by an alkyl radical on the nitrogen
atom), it being understood that the alkyl radicals
and alkyl moieties referring to the symbols of the
general formula (V) contain 1 to 5 carbon atoms
and form a linear or branched chain.

Some of the derivatives of synergistins of general
formula (V) can have isomeric forms. It is to be under-
stood that these isomeric forms as well as their mixtures
can be advantageously associated with the products of
general formula (I).

The products of general formula (V) defined as above
under (1), with the exception of those in which R₂ de-
notes a formyl or alkylcarbonyl radical, can be prepared
by the action of an amine of general formula:



in which R₂ and R₃ are defined as above, on a synergis-
tin of general formula:



in which Y denotes a hydrogen atom (virginiamycin S) or the dimethylamino radical (pristinamycin I_A), in the presence of an alkali metal cyanoborohydride.

The operation is generally carried out with an excess of amine of general formula (VIII) in the presence of an alkali metal cyanoborohydride such as sodium cyanoborohydride, in an organic solvent such as an alcohol containing dissolved gaseous hydrogen chloride (methanolic hydrogen chloride or ethanolic hydrogen chloride) at a temperature between 0° C. and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20° C.

The reaction can be advantageously carried out in the presence of a drying agent such as molecular sieves.

The products of general formula (V) defined as above under (1) in which R² denotes a formyl or alkylcarbonyl radical and R₃ denotes an alkyl radical substituted by a carboxy, alkylamino or dialkylamino radical whose alkyl radicals optionally form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, alkyl-piperazinyl or azepinyl ring, or denotes a saturated 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these heterocyclic rings being capable of being substituted by an alkyl radical on the nitrogen atom, and Y is defined as above, can be prepared by the action of a product of general formula:



(X)

in which R₆ denotes a hydrogen atom or an alkyl radical and Q denotes a halogen atom or an alkylcarbonyloxy radical, on a product of general formula:

20 in which Y is defined as before and R'3 has the corresponding definition of R₃ which is given above.

The reaction is usually carried out in an organic solvent such as pyridine, in a chlorinated solvent (methylene chloride) or an ether (tetrahydrofuran) in the presence of an acid acceptor such as an organic base such as triethylamine or an inorganic base such as an alkali metal carbonate or bicarbonate such as sodium bicarbonate, the operation being carried out at a temperature between 0° and 80° C.

35 It is to be understood that, when R'3 denotes a radical containing a secondary amine group, the said group must be protected before the product of general formula 40 (X) is reacted with the product of general formula (XI). The protection is carried out under the conditions described earlier for the preparation of the product of the 45 general formula (II).

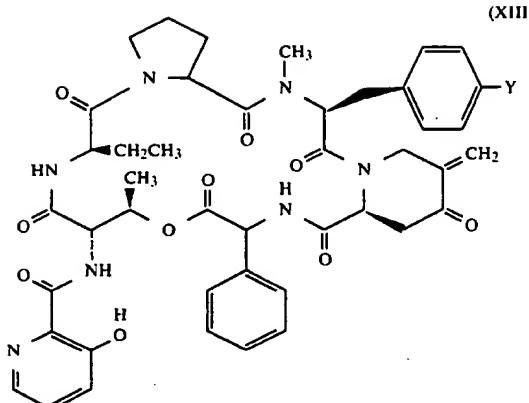
It is also to be understood that, when R₂ and/or R₃ in the general formula (VIII) denote a radical containing a secondary amine group, the latter must be protected beforehand, before the product of general formula (VIII) is reacted with the product of general formula (IX). The blocking and the deblocking are carried out 55 as described earlier.

The products of general formula (V) defined as before under (2), in which Y is defined as before and the other symbols are defined as before under (2) (a) can be prepared by the action of a product of general formula:



(XII)

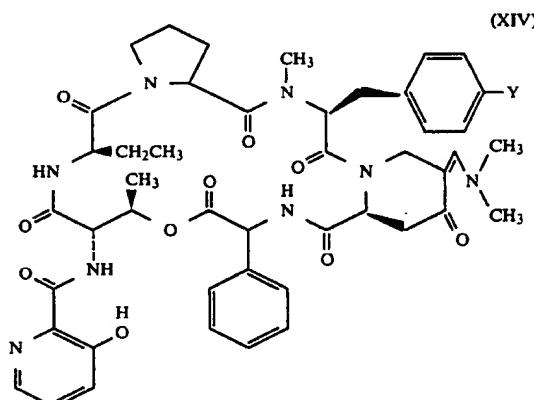
65 in which R'4 has the definition of R₄ given earlier under (2) (a), on the product of general formula:



in which Y is defined as before.

The operation is usually carried out in an organic solvent such as an alcohol such as methanol, or a chlorinated solvent such as chloroform, or a mixture of these solvents, at a temperature between 0° C. and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20° C.

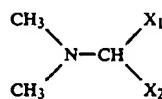
The products of general formula (XIII) can be prepared by the action of an alkali metal borohydride such as sodium cyanoborohydride on a product of general formula:



in which Y is defined as before.

The operation is usually carried out in an organic solvent such as an ether such as tetrahydrofuran, or an alcohol, for example isopropanol, in the presence of an acid such as trifluoroacetic acid, at a temperature between 0° C. and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20° C.

The products of general formula (XIV) can be obtained by the action of a product of formula:



in which either X₁ denotes an alkyloxy radical and X₂ denotes an alkyloxy or dimethylamino radical, or X₁

and X₂ both denote a dimethylamino radical, on a product of general formula (IX).

In practice, it is advantageous to react tertbutoxybis(dimethylamino)methane with the product of general formula (IX), the operation being carried out in an organic solvent such as a chlorinated solvent such as 1,2-dichloroethane, or an amide (for example dimethylformamide) at a temperature between 0° and 80° C., preferably at a temperature in the region of 20° C.

10 The products of general formula (XV) can be prepared according to the methods described by H. Bredebeck et al., Chem. Ber., 101, 41 and 3058 (1968) and Chem. Ber., 106, 3725 (1973).

15 The products of general formula (V) in which Y is defined as before and the other symbols are defined as earlier under (2) (b), except for R₄ denoting a 3-pyrrolidinyloxy, 3- or 4-piperidyloxy or alkyloxy radical, optionally substituted as defined under (2) (b), can be prepared by the action of a product of general formula:



in which R''4 has the definition of R₄ given above, on a product of general formula (XIV) in which Y is defined as earlier.

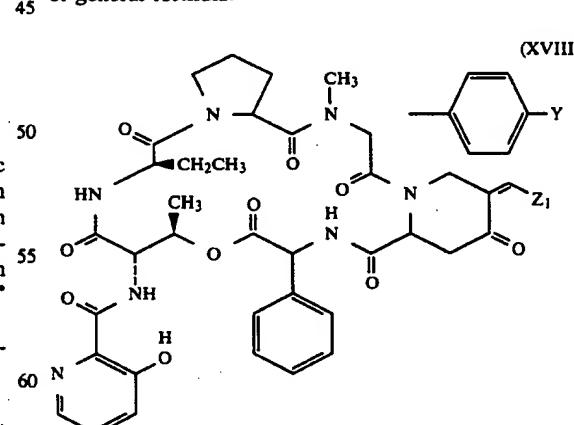
25 The reaction is carried out in an organic medium in the presence of an acid (for example acetic acid or a mixture of acetic acid with catalytic quantities of trifluoroacetic acid), in the presence or absence of a solvent, at a temperature between 0° and 50° C.; preferably at a temperature in the region of 20° C.

30 Where applicable, the solvent can be chosen from organic solvents such as ethers (tetrahydrofuran), alcohols (ethanol) and chlorinated solvents (methylene chloride or chloroform, for example).

35 The products of general formula (V) in which Y is defined as before and the other symbols are defined as earlier under (2) (b) can be prepared by the action of a product of general formula:



40 in which R'''4 is defined as R₄ under (2) (b), on a product of general formula:



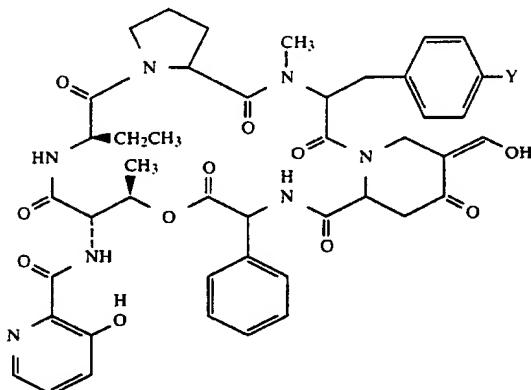
50 in which Y is defined as before and Z₁ denotes a tosylate, acetoxy, trimethylsilyloxy or dialkylxyphenoxy radical whose alkyl moieties contain 1 to 4 carbon atoms forming a linear or branched chain or Z₁ denotes a chlorine atom.

The operation is usually carried out in an organic solvent such as ether such as tetrahydrofuran, an alcohol such as ethanol, or a chlorinated solvent (methylene chloride or chloroform, for example) at a temperature in the region of 20° C. The reaction is carried out in a basic medium, for example in the presence of an alkali metal hydride or an alkali metal alcoholate such as sodium ethoxide or potassium tert-butoxide.

When R'''4 is different from a substituted alkyloxy or (heterocyclic ring radical)oxy radical, it is also possible to operate either in a neutral medium at a temperature between 0° and 50° C., in one of the solvents mentioned above, or in an acetic medium under conditions identical to those described earlier for the action of a product of general formula (XVI) on a product of general formula (XIV).

The products of general formula (XVIII) can be prepared by acid hydrolysis of a product of general formula (XIV) to obtain a product of general formula:

(XIX)



followed:

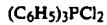
(α) either by the action of a product of general formula:



(XX)

in which X denotes a halogen atom and Z'_1 has the definition given before for Z_1, except for denoting a chlorine atom

(β) or by the action of a product of formula:



(XXI)

to obtain a product of general formula (XVIII) in which Z_1 denotes a chlorine atom.

The hydrolysis of the product of general formula (XIV) to the product of general formula (XVIII) is carried out by means of an aqueous solution of an inorganic acid such as a 0.1N aqueous solution of hydrochloric acid, the operation being carried out at a temperature in the region of 20° C. The reaction of the product of general formula (XX) with the product of general formula (XIX) is generally carried out in an organic solvent such as methylene chloride in the presence of an acid-acceptor such as an organic base such as triethylamine, or an inorganic base such as an alkali metal carbonate or bicarbonate, for example sodium or potassium bicarbonate. The operation is generally carried out at a temperature between -20° and +20° C.

The reaction of the product of general formula (XXI) with the product of general formula (XIX) is usually carried out in a chlorinated solvent such as methylene chloride at a temperature between -20° and +20° C.

The products of general formulae (III), (VIII), (XII), (XVI) and (XVII) can be prepared according to, or in a similar manner to, the methods described in the examples below, and especially according to:

- G. G. Urquart et al., Org. Synth., 21, 36 (1941)
- A. I. Vogel, J. Chem. Soc., 1822 (1948)
- J. H. Chapman and L. N. Owen, J. Chem. Soc., 579 (1950)
- H. R. Snyder et al., J. Am. Chem. Soc., 69, 2672 (1947)
- D. D. Reynolds et al., J. Org. Chem., 26, 5125 (1961)
- J. W. Haefele et al., Proc. Sci. Toilet Goods Assoc., 32, 52 (1959)
- H. Barrer et al., J. Org. Chem., 27, 641 (1962)
- J. H. Biel et al., J. Amer. Chem. Soc., 77, 2250 (1955) when dealing with a product of general formula (III), (XII), (XVI) or (XVII) in which R, R'4, R''4 or R'''4 denotes a substituted alkylthio or (heterocyclic ring radical)thio radical, or according to:
- A. J. W. Headlee et al., J. Amer. Chem. Soc., 55, 1066 (1933)
- B. K. Campbell and K. N. Campbell, J. Amer. Chem. Soc., 60, 1372 (1938)
- R. C. Elderfield et al., J. Amer. Chem. Soc., 68, 1579 (1946)
- when dealing with a product of general formula (XIV) or (XVII) in which R''4 or R'''4 denotes a substituted alkyloxy or (heterocyclic ring radical)oxy radical, or according to:
- J. Amer. Chem. Soc., 54, 1499 (1932) and
- J. Amer. Chem. Soc., 54, 3441 (1932), when dealing with a product of general formula (VIII) or of general formula (III), (XVI) or (XVII) in which R, R'4 or R''4 are substituted alkylamino radicals, or according to:
- E. F. Elslager et al., J. Med. Chem., 17, 99 (1974)
- L. M. Werbel et al., J. Het. Chem., 10, 363 (1973) when dealing with a product of general formula (III), (XVI) or (XVII) in which R, R'4 or R''4 are (heterocyclic ring radical)amino radicals.

It is to be understood that in the above methods, when R, R_2, R_3, R'4, R''4 or R'''4 contain a secondary amine group capable of interfering with the reaction, this must first be protected by any known method which does not affect the remainder of the molecule.

The protective radical is removed after reaction under the conditions described earlier.

Where applicable, the isomers of the products of general formula (I) and/or the products of general formula (V) can be separated by chromatography or by high performance liquid chromatography.

The products of general formula (V) can be purified as mentioned earlier for the products of general formula (I).

The pristinamycin II_B derivatives of formula (I) and their pharmaceutically acceptable salts exhibit particularly advantageous antibacterial properties in vitro and in vivo.

In vitro, the products of formula (I) have shown themselves to be active towards *Staphylococcus aureus* Smith at concentrations from 4 to 100 µg/cm³. In addition, they have a synergistic effect on the antibacterial action of pristinamycin I_A in concentrations greater than 0.1 and 10 µg/cm³.

In vivo, the products of formula (I) have shown themselves to be active in the mouse in experimental infections with *Staphylococcus aureus* Smith at dosages between 40 mg/kg and dosages greater than 300 mg/kg by the subcutaneous route. When they are combined with pristinamycin I_A in proportions from 10-90% to 90-10%, they have a synergistic effect on the antimicrobial action at dosages between 8 and 200 mg/kg by the subcutaneous route.

The acute toxicity of the products of formula (I), expressed as their LD₅₀, is generally between 300 mg/kg and dosages greater than 1 g/kg by the subcutaneous route in the mouse.

The products of special interest are those of formula (I) in which the symbol R denotes:
 either a nitrogen-containing 5 or 6-membered heterocyclic ring radical unsubstituted or substituted by an alkyl radical,
 or an alkyl chain of 2 to 4 carbon atoms and substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, and N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, alkylamino, dialkylamino, dialkylcarbamoyloxy (the alkyl moieties of these two latter radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, a saturated or unsaturated 5 or 6-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulfoxide or sulphone, and unsubstituted or substituted by alkyl), or substituted by a nitrogen-containing 5 or 6-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulfoxide or sulphone and unsubstituted or substituted by alkyl, this heterocyclic ring being linked to the alkyl by a carbon atom of the ring, it being understood that at least one of the substituents carried by the above alkyl chain is a nitrogen-containing substituent capable of forming salts, and n is 1 or 2; and, among these products, those which are especially active are the products of formula (I) in which R denotes an alkyl chain containing 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 5 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 5 or 6 ring atoms, alkylamino of 1 to 4 carbon atoms, and dialkylamino (in which the alkyl moieties contain 1 to 3 carbon atoms each or form, with the nitrogen atom to which they are attached, a saturated 5 or 6-membered heterocyclic ring), or R denotes a nitrogen-containing 5 or 6-membered heterocyclic ring unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the alkyl chain being a nitrogen-containing substituent capable of forming salts, and at least one of the radicals carried by this chain is placed in a 1- or 2-position, and n is 1 or 2.

The following derivatives of pristinamycin II_B of formula (I) are of especial interest.

26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin II_B

26-[(2R)-2-dimethylaminobutyl]sulphonylpristinamycin II_B

26-(2-diethylaminopropyl)sulphonylpristinamycin II_B

26-(2-diisopropylaminoethyl)sulphonylpristinamycin II_B.

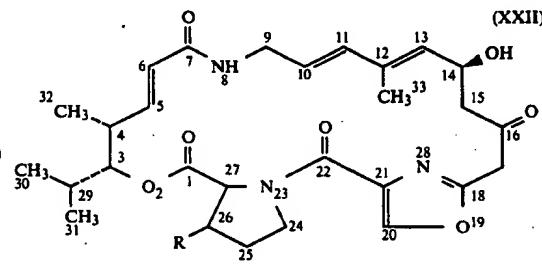
For use in therapy, the compounds of formula (I) can be used as such, that is to say in the form of the base, in combination with already known synergistins, but,

since the chief advantage of the products of the invention is their solubility in water, it is especially advantageous to use them in the form of pharmaceutically acceptable salts, in combination with known synergistins or with the synergistins of formula (V), dissolved either in the form of pharmaceutically acceptable salts or, where applicable, in the form of the base when the solubility is sufficient for the solution produced to contain (in a volume suitable for a single dose) a quantity of active ingredient which is at least equal to the therapeutically active dose.

Both for the products of formula (I) and for the products of formula (V), the pharmaceutically acceptable salts which can be mentioned are the salts of addition with inorganic acids such as hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, or with organic acids, such as acetates, propionates, succinates, maleates, fumarates, methanesulphonates, p-toluenesulphonates, isethionates, or substitution derivatives of these compounds. There can also be mentioned, as pharmaceutically acceptable salts, the salts with alkali metals (such as sodium and potassium salts), with alkaline-earth metals (such as the magnesium salt), the ammonium salt and salts of addition with nitrogen-containing organic bases (ethanolamine, diethanolamine, trimethylamine, triethylamine, methylamine, propylamine, diisopropylamine, N,N-dimethylethanolamine, benzylamine, dibenzylamine, dicyclohexylbenzylamine, N-benzyl-β-phenethylamine, N,N'-dibenzylmethylenediamine, benzhydrylamine, arginine, leucine, lysine or N-methylglucamine).

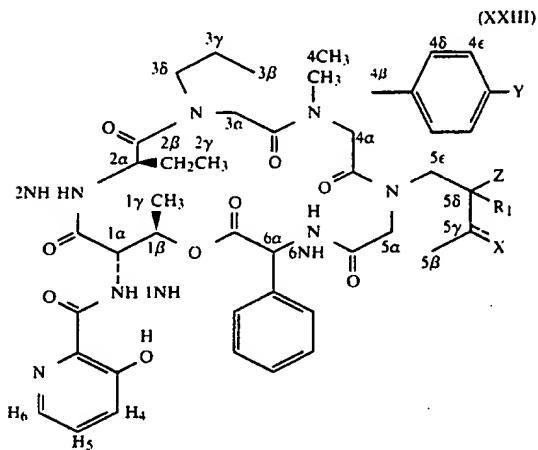
Quaternary ammonium salts corresponding to the anions listed above can be mentioned as pharmaceutically acceptable salts for the products of general formula (V) in which Z denotes a radical of general formula (VII) in which R₄ denotes a trialkylammonio radical.

The following examples, given without implying any limitation, show how the invention can be put into practice. The NMR spectra of the products illustrated in these examples and in the reference examples which follow, show general characteristics which are common to all the products of general formula (I) or of general formula (V) and individual characteristics which are specific to each of the products, depending on the substituents. Only the individual characteristics due to the changeable radicals are mentioned in the examples or reference examples which follow. For the products of general formula (I), all the protons are designated according to the numbering indicated in the following formula:



For the synergistins of general formula (V) all the protons are designated according to the numbering indicated in the general formula (XXIII); this number-

ing is that recommended by J. O. Anteunis et al., [Eur. J. Biochem., 58, 259 (1975)].



Unless stated otherwise, all the spectra were recorded at 250 MHz in deuteriochloroform; the chemical shifts are expressed in ppm relative to the tetramethylsilane signal. The abbreviations used in the following text are as follows:

s=singlet

d=doublet

t=triplet

mt=multiplet

m = unresolved bands

dd=doublet of doublets

dt=doublet of triplets

ddd=doublet of doublets of doublets

It is to be understood that the various isomers have

It is to be understood that the various isomers have been classified arbitrarily according to the chemical shifts observed in NMR.

The names isomer A₁ and isomer A₂ of the products of general formula (I) in which n=1 are given to the isomers which have the characteristics: approximately 1.7 (s, —CH₃ at 33); approximately 3.8 (s, >CH₂ at 17); <5 (d, —H₂₇) isomer A₂ or >5 (d, —H₂₇) isomer A₁; approximately 5.50 (broad d, —H₁₃); approximately 6.20 (d, —H₁₁); approximately 6.6 (>NH at 8); >8 (s, —H₂₀).

The names isomer B₁ and isomer B₂ of the products of general formula (I) in which n=1 are given to the isomers which have the characteristics: approximately 1.5 (s, —CH₃ at 33); approximately 3.7 and 3.9 (2d, >CH₂ at 17); approximately 4.8 (mt, —H₁₃); <5 (d, —H₂₇) isomer B₂ or >5 (d, —H₂₇) isomer B₁; approximately 5.70 (borderline AB, —H₁₁ and —H₁₀); approximately 5.7.7 (>NH at 8); approximately 7.8 (s, —H₂₀). 50 55

The name isomer A of the product of general formula (II) is given to the isomer which has NMR characteristics identical to those listed above for the isomers A₁ and A₂ of the products of general formula (I), it being understood that the H at 27 is characterized by: 4.7 (d, $J \leq 1$ Hz).

The name isomer B of the product of general formula (II) is given to the isomer which has NMR characteristics identical to those listed above for the isomers B₁ and B₂ of the products of general formula (I), it being understood that the H at 27 is characterized by: 4.6 (d, $J \leq 2.5$ Hz).

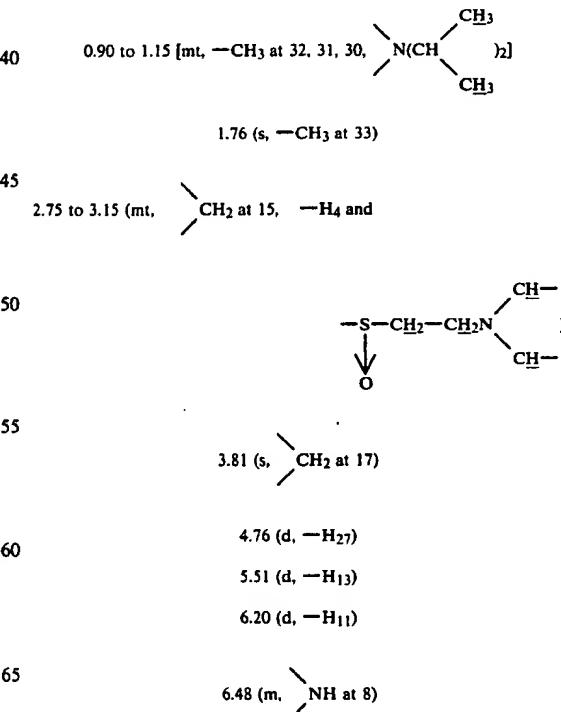
In the following examples, the name "flash" chromatography is given to a purification technique in which a short chromatography column is used and operated under an intermediate pressure (50 kPa) with the use of a silica with a particle size distribution of 40–53 µm, according to W. C. Still, M. Kahn and A. Mitra (*J. Org. Chem.* 43, 2923 (1978)).

In the examples described below, unless stated otherwise, all the products can be dissolved at a strength of at least 2%, in the form of hydrochloride.

EXAMPLE 1

15 Trifluoroacetic acid (0.4 cc), and then 85% meta-chlorobenzoic acid (1.06 g) are added, under a nitrogen atmosphere; while the temperature is maintained at 0° C., to 26-(2-diisopropylaminoethyl)thiopristinamycin II_B (isomer A) (3.59 g) dissolved in dichloromethane (40 cc) at 0° C. After 20 hours' stirring at 25° C., the reaction mixture is added to a saturated aqueous solution of sodium bicarbonate. The organic phase is separated off and then the aqueous phase is washed with methylene chloride (3×100 cc). The organic phase are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 25 30° C. to give a yellow solid (4.2 g) which is purified by "flash" chromatography [(eluent: chloroform-methanol (90-10 by volume)], 20-cc fractions being collected. Fractions 22 to 28 are combined and concentrations to 30 dryness under reduced pressure (2.7 kPa) at 30° C., to give a light-yellow solid, which is stirred in ethyl ether (10 cc). The solid obtained is separated off by filtration to give 26-(2-diisopropylaminoethyl)sulphinylpristinamycin II_B (isomer A₂) (0.62 g) in the form of a yellow powder melting at about 155° C.

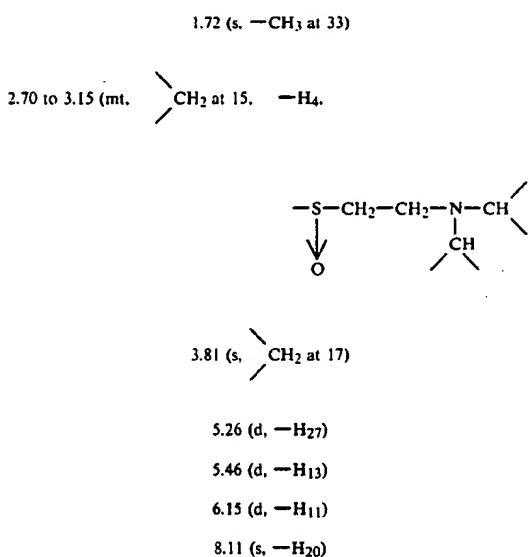
NMR spectrum:



-continued
8.13 (s, —H₂₀)

Fractions 35 to 45 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give a light-yellow solid which is stirred in ethyl ether (15 cc). The solid obtained is separated off by filtration to give 26-(2-diisopropylaminoethyl)sulphinylpristinamycin II_B (80% isomer A₁, 20% isomer A₂) (1.07 g) in the form of a light-yellow powder melting at about 145° C.

NMR spectrum (isomer A₁):

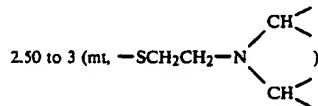


26-(2-Diisopropylaminoethyl)thiopristinamycin II_B can be prepared as follows:

2-Diisopropylaminoethanethiol (16 g) dissolved in dichloromethane (30 cc) is added dropwise under a nitrogen atmosphere to pristinamycin II_A (52 g) dissolved in a mixture of dichloromethane (260 cc) and methanol (520 cc), at -30° C. The solution is stirred at -20° C. for 20 hours and then concentrated under reduced pressure (2.7 kPa) at 30° C. The solid obtained is stirred with ethyl ether (2 × 1000 cc), separated off by filtration and then crystallized from acetonitrile (100 cc). The crystals are separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. In this manner, 26-(2-diisopropylaminoethyl)thiopristinamycin II_B (isomer A) (33.6 g) is obtained in the form of white crystals melting at about 122° C.

NMR spectrum:

1 to 1.15 (mt, isopropyl-CH₃)
1.72 (s, —CH₃ at 33)
1.80 to 2.20 (mt, —H₂₅, —H₂₉)



-continued

3.40 (broad d, —H₂₆)
4.74 (broad s, —H₂₇)
6.32 (m, —NH₈)
8.15 (s, —H₂₀)

2-Diisopropylaminoethanethiol can be prepared according to the method described by D. D. Reynolds, D. L. Fields and D. L. Johnson, J. Org. Chem. 26, 5125 (1961).

EXAMPLE 2

Sodium bicarbonate (1.22 g) is added to 26-(2-diisopropylaminoethyl)thiopristinamycin II_B (isomer A) (10 g) dissolved in chloroform (300 cc). The mixture is cooled to -50° C. and 98% meta-chloroperbenzoic acid (2.98 g) dissolved in chloroform (100 cc) is added dropwise. The mixture is stirred at -50° C. for 2 hours 15 minutes and then a saturated aqueous solution of sodium bicarbonate is added to it. After 15 minutes' stirring at 25° C., the mixture is separated and then the aqueous phase is washed with dichloromethane (3 × 200 cc). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give a whitish porous solid (10.62 g). The latter is dissolved in ethyl acetate (400 cc) and then treated with a 0.1N aqueous solution of hydrochloric acid (140 cc). The pH of the aqueous solution is then adjusted to 4.2 by adding a pH 4.2 buffer (400 cc). The aqueous phase is separated off and then the organic phase is washed with pH 4.2 buffer (400 cc). The aqueous phases are combined and washed with ethyl acetate (2 × 150 cc). After separation, the aqueous phase is adjusted to pH 7-8 adding sodium bicarbonate and is then washed with dichloromethane (3 × 300 cc). The organic phases are combined and then washed with pH 7.5 buffer (2 × 200 cc). The aqueous phase is washed with dichloromethane (50 cc) and then the organic phases are combined, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C., to give a light-yellow solid (8.04 g), which is stirred in ethyl ether (100 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. 40 In this manner, 26-(2-diisopropylaminoethyl)sulphinylpristinamycin II_B (isomer A₂) (7.5 g) is obtained in the form of a yellow powder melting at about 158° C., the NMR characteristics of which are identical to those in Example 1.

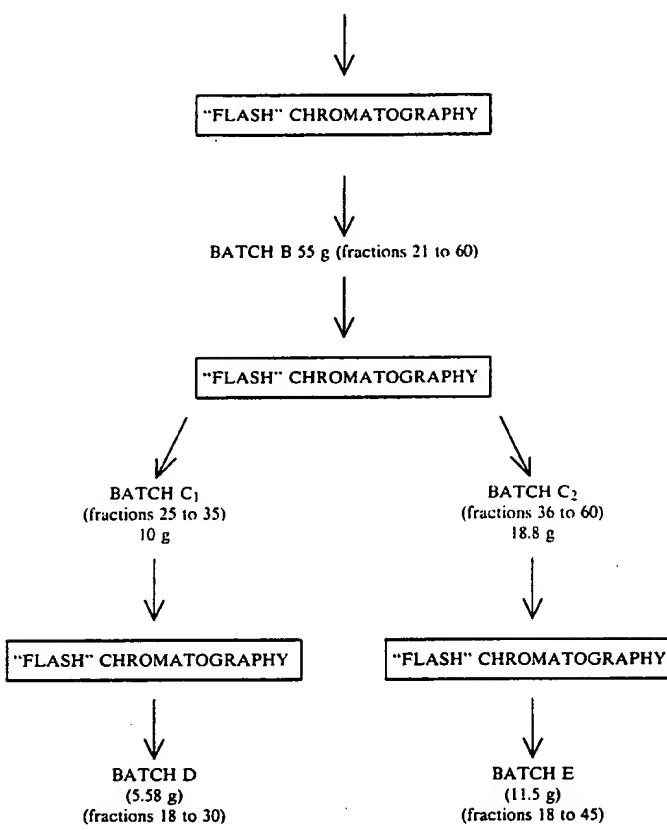
EXAMPLE 3

The method used is that described in Example 1, but starting with 26-(2-diethylaminoethyl)thiopristinamycin II_B (53.2 g), trifluoroacetic acid (6.25 cc) and meta-chloroperbenzoic acid (16.4 g). Three successive purifications by "flash" chromatography are carried out [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, according to the following scheme:

Purification scheme

BATCH A (68 g)

-continued

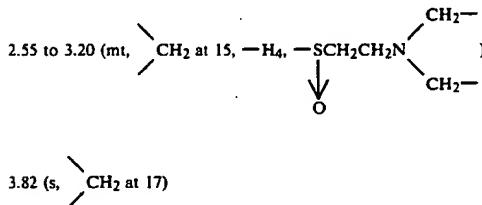
Purification scheme

In all cases, the fractions recovered are concentrated to dryness under reduced pressure (2.7 kPa) at 30° C.

Batch D is stirred in ethyl ether (60 cc). The solid obtained is separated off by filtration. 26-(2-Diethylaminoethyl)sulphinylpristinamycin II_B (isomer A₂) (5 g) is obtained in the form of a yellow powder melting at about 172° C.

NMR spectrum:

1.00 to 1.14 (mt, —CH₃ at 32 + chain CH₃)
1.75 (s, —CH₃ at 33)



4.81 (d, —H₂₇)
5.51 (d, —H₁₃)
6.19 (d, —H₁₁)

6.46 (dd, NH at 8)

8.13 (s, —H₂₀)

Batch E is stirred in ethyl ether (10 cc). The solid obtained is separated off by filtration. 26-(2-Diethylaminoethyl)sulphinylpristinamycin II_B (60% isomer A₂), 15% isomer A₁, 12% isomer B₁, 13% isomer B₂) (10.9 g) is obtained.

NMR spectrum: 1.00 to 1.13 (mt, —CH₃ at 32 and —N(CH₂CH₃)₂ of A₁ and A₂), 1.54 (s, —CH₃ at 33 of B₁ and B₂), 1.68 (s, —CH₃ at 33 of A₁), 1.75 (s, —CH₃ at 33 of A₂), 2.65 to 2.95 (mt, —S(O)CH₂CH₂N< and H₄ of A₁) 2.55 to 3.20 (mt, >CH₂ at 15, —H₄ and —S(O)CH₂CH₂N< of A₂), 3.77 (borderline AB, >CH₂ at 17 of A₁), 3.82 (s, >CH₂ at 17 of A₂), 4.81 (d, —H₂₇ of A₂), 5.24 and 5.25 (2d, —H₂₇ of A₁ and of B₁), 5.41 (d, —H₁₃ of A₁), 5.51 (d, —H₁₃ of A₂), 5.99 and 6 (2d, —H₆ of B₁ and —H₆ of B₂), 6.11 (d, —H₁₁ of A₁), 6.19 (d, —H₁₁ of A₂), 6.46 (dd, >NH at 8 of A₂), 6.79 (dd, >NH at 8 of A₁), 7.82 (s, —H₂₀ of B₁ and B₂), 8.12 (s, —H₂₀ of A₁), 8.13 (s, —H₂₀ of A₂).

26-(2-Diethylaminoethyl)thiopristinamycin II_B can be prepared as follows: A solution of diethylaminoethanethiol (3.7 g) in methylene chloride (15 cc) is added to a suspension of pristinamycin II_A (13.1 g) in methanol (150 cc). The solution obtained is stirred at a temperature of about 20° C. for 18 hours and is then poured into distilled water (1500 cc); the mixture obtained is extracted 3 times with methylene chloride (1000 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]; after

fractions 5 to 23 have been concentrated to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-dimethylaminoethyl)thiopristinamycin II_B (12.4 g) is obtained in the form of a yellow powder melting at about 105° C.

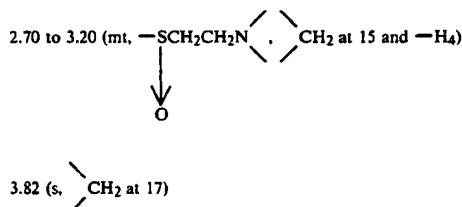
NMR spectrum: 1.05 (m, —N(CH₂CH₃)₂+—H₃₃), 1.70 (s, —H₃₃), 1.85 to 2.15 (m, —H₂₅, —H₂₉), 2.60 (q, —N(CH₂CH₃)₂), 2.75 (s, —S—CH₂CH₂—), 2.9 (dd, ABX system, —H₁₅), 3.10 (dd, ABX system, —H₁₅), 3.40 (ddd, —H₂₆), 3.80 (s, —H₁₇), 4.75 (d, —H₂₇), 5.50 (d, —H₁₃), 6.15 (d, —H₁₁), 6.60 (broad s, >NH at 8), 8.10 (s, —H₂₀).

EXAMPLE 4

By using a method similar to that described in Example 1, but starting from 26-(2-dimethylaminoethyl)thiopristinamycin II_B (5.5 g), trifluoroacetic acid (0.67 cc) meta-chloroperbenzoic acid (1.8 g), and after a purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 30-cc fractions being collected, and concentrating fractions 23 to 40 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-dimethylaminoethyl)sulphinylpristinamycin II_B (70% isomer A₂, 15% isomer A₁, 7% isomer B₁, 8% isomer B₂) (0.4 g) is obtained in the form of a yellow powder melting at about 150° C.

NMR spectrum (isomer A₂):

1.77 (s, —CH₃ at 33)
2.41 (s, —N(CH₃)₂)



4.84 (mt, —H₃ and —H₂₇)
5.52 (d, —H₁₃)
6.19 (d, —H₁₁)

6.42 (m, —NH at 8)

8.14 (s, —H₂₀)

26-(2-Dimethylaminoethyl)thiopristinamycin II_B can be prepared as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (2.7 g) and 2-dimethylaminoethanethiol (0.58 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 11 to 17 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-dimethylaminoethyl)thiopristinamycin II_B (1.1 g) is obtained in the form of a yellow powder melting at about 100° C.

NMR spectrum: 2.35 (s, 6H: —N(CH₃)₂), 2.80 (m, 4H: —S—CH₂CH₂—N<), 3.40 (ddd, 1H: —H₂₆), 4.75 (d, 1H: —H₂₇), 8.10 (s, 1H: —H₂₀).

EXAMPLE 5

By using the same method as that described in Example 2, but starting from 26-(2-N-methyl-N-ethylamino-

ethyl)thiopristinamycin II_B (90% isomer A 10% isomer B), (4.7 g), sodium bicarbonate (1.22 g), and 98% meta-chloroperbenzoic acid (1.41 g), and after purification by "flash" chromatography [eluent: dichloromethane-methanol (90-10 by volume)], 20-cc fractions being collected, and concentrating fractions 44 to 52 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (2.47 g) is obtained, which is stirred in ethyl ether (50 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. In this manner, 2-(N-methyl-N-ethyl-2-aminoethyl)sulphinylpristinamycin II_B (isomer A₂) (2.3 g) is obtained in the form of a yellow powder melting at about 145° C.

NMR spectrum

1.09 (t, —N—CH₂—CH₃)

1.76 (s, —CH₃ at 33)

2.31 (s, —N—CH₃)

2.54 (mt, —N—CH₂CH₃)

2.80 (mt, —H₄)

2.70 to 3.10 (mt, —S—CH₂—CH₂N(—CH₂CH₃)₂—)
↓
3.82 (s, —CH₂ at 17)

2.92 to 3.12 (2dd, —CH₂ at 15)

3.24 (mt, —H₂₆)

3.82 (s, —CH₂ at 17)

4.82 (s, —H₂₇)

5.51 (d, —H₁₃)

6.40 (dd, —NH at 8)

8.13 (s, —H₂₀)

26-(N-Methyl-N-ethyl-2-aminoethyl)thiopristinamycin II_B (90% isomer A, 10% isomer B) can be prepared by using the same procedure as that described in Example 1, but starting from pristinamycin II_A (14.11 g) and N-methyl-N-ethyl-2-aminoethanethiol (3.2 g). After stirring for 4 days at -20° C. and purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 80-cc fractions being collected, followed by concentration of fractions 25 to 48 to dryness under reduced pressure (2.7 kPa) at 30° C., a yel-

31

low solid (4.75 g) is obtained, which is dried under reduced pressure (90 kPa) at 40° C. In this manner, 26-(N-methyl-N-ethyl-2-aminoethyl)thiopristinamycin II_B (90% isomer A, 10% isomer B) (4.7 g) is obtained in the form of a yellow powder melting at about 140° C.

NMR spectrum: 1.1 (mt, CH₂CH₃), 1.73 (s, CH₃ at 33), 2.30 (s, >N—CH₃), 2.45 to 2.6 (mt, >N—CH₂CH₃), 2.68 to 2.78 (2mt, —S—CH₂—CH₂N<), 2.78 (mt, —H₄), 2.90 and 3.12 (2dd, —CH₂— at 15), 3.40 (d, —H₂₆), 3.83 (s, —CH₂— at 17), 4.76 (s, —H₂₇), 5.48 (d, —H₁₃), 6.14 (d, —H₁₁), 6.34 (mf, >NH at 8), 8.11 (s, —H₂₀).

N-Methyl-N-ethyl-2-aminoethanethiol can be obtained by a method similar to that described by D. D. Reynolds et al., J. Org. Chem. 26, 5125 (1961), from N-methyl-N-ethylamine (25 g) and ethylene thiocarbonate (43.7 g). After distillation, N-methyl-N-ethyl-2-aminoethanethiol (1.3 g) is obtained in the form of a colourless liquid.

[B.p. (6.7 kPa)=52° C.]

EXAMPLE 6

Using a method similar to that described in Example 1, but starting from 26-(3-dimethylaminopropyl)thiopristinamycin II_B (50:50 A/B isomers) (9.8 g), trifluoroacetic acid (1.18 cc) and meta-chloroperbenzoic acid (3.1 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (80-20 by volume)], 15-cc fractions being collected, and concentrating fractions 53 to 75 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(3-dimethylaminopropyl)sulphinylpristinamycin II_B (mixed isomers) (1.6 g) is obtained in the form of a yellow powder melting at about 165° C.

NMR spectrum (mixture of isomers of type A₂≈45%, B₂≈35% and B₁≈15%): 1.53 (s, —CH₃ at 33 B₂ and B₁), 1.75 (s, —CH₃ at 33 of A₂), 2.26, 2.28 and 2.32 (3s, >NCH₃ of the 3 isomers), 3.82 (s, >CH₂ at 17 of A₂), 3.70 and 3.88 (2d, >CH₂ at 17 of B₁), 3.69 and 3.91 (2d, >CH₂ at 17 of B₂), 4.76 (d, —H₂₇ of B₂), 5.25 (d, —H₂₇ of B₁), 5.50 (d, —H₁₃ of A₂), 7.63 (mt, >NH at 8 of B₂), 7.74 (mt, >NH at 8 of B₁), 7.82 (s, —H₂₀ of B₂ and B₁), 8.14 (s, —H₂₀ of A₂). 26-(3-Dimethylaminopropyl)thiopristinamycin II_B can be obtained as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (5.25 g) and 3-dimethyl-aminopropanethiol (1.3 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 6 to 29 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(3-dimethylaminopropyl)thiopristinamycin II_B (3.3 g) is obtained in the form of a yellow powder melting at about 100° C.

NMR spectrum:

1.50 (s, 3H × 0.5: —H₃₃ 1st isomer)
1.70 (s, 3H × 0.5: —H₃₃ 2nd isomer)

1.80 (m, 2H: —SCH₂—CH₂—CH₂N<)

2.20 (s, 6H × 0.5: —N(CH₃)₂ 1st isomer)
2.25 (s, 6H × 0.5: —N(CH₃)₂ 2nd isomer)

2.40 (m, 2H: —SCH₂—CH₂—CH₂N<)

32

-continued

2.70	(m, 2H: —SCH ₂ —CH ₂ —CH ₂ N<)
3.35	{ (2m, 1H: —H ₂₆ of each isomer)
3.45	{ (2d, 1H: —H ₂₇ of each isomer)
4.60	{ (2s, 1H: —H ₂₀ of each isomer)
4.70	
7.80	
8.10	

EXAMPLE 7

By using a method similar to that described in Example 1, but starting from 26-(2-diethylaminopropyl)thiopristinamycin II_B (6.3 g), trifluoroacetic acid (0.72 cc) and meta-chloroperbenzoic acid (1.91 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 volume)], 60-cc fractions being collected, and after concentrating fractions 7 to 9 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-diethylaminopropyl)sulphinylpristinamycin II_B (isomers A₂) (0.99 g) is obtained in the form of a yellow powder melting at about 150° C.

NMR spectrum: 1.03 to 1.20 (mt, —CH₂—CH(CH₃)N(CH₂CH₃)₂), CH₃ at 32), 1.76 (s, —CH₃ at 33), 3.82 (s, CH₂ at 17), 4.79 (m, —H₂₇), 5.53 (d, —H₁₃), 6.20 (d, —H₁₁), 6.42 (m, >NH at 8), 8.13 (s, —H₂₀).

After concentrating fractions 23 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-diethylaminopropyl)sulphinylpristinamycin II_B (isomers A₁) (0.64 g) is obtained in the form of a beige-yellow powder melting at about 160°-170° C.

NMR spectrum:

1.14 (mt, —N(CH₂CH₃)₂)
1.24 (broad d, CH₃—CH—N<)

1.73 (s, —CH₃ at 33)

3.81 (borderline AB, CH₂ at 17)

5.28 (d, —H₂₇)
5.43 (d, —H₁₃)
6.15 (d, —H₁₁)

6.88 (m, NH at 8)

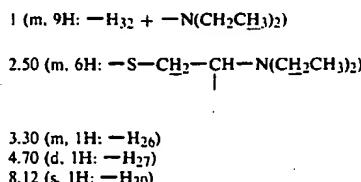
8.10 (s, —H₂₀)

26-(2-Diethylaminopropyl)thiopristinamycin II_B can be prepared as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (3.15 g) and 2-diethylaminopropanethiol (1.8 g), and after purification by "flash" chromatography [eluent: methylene

chloride-methanol (90-10 by volume)], 20-cc fractions being collected, and concentrating fractions 3 to 5 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-diethylaminopropyl)thiopristinamycin II_B (1.4 g) is obtained in the form of a yellow powder melting at about 160° C.

NMR spectrum:



2-(Diethylaminopropanethiol can be prepared as follows:

A 10N aqueous solution of sodium hydroxide (25 cc) is added to a solution of 3-S-isothioureido-2-diethylaminopropane dihydrochloride (29.5 g) in distilled water (150 cc). The mixture is heated to 100° C. for 1 hour, cooled to 20° C., adjusted to pH 9 by adding a 12N aqueous solution of hydrochloric acid (8 cc), and is then extracted with ethyl ether (3 × 100 cc). The ether phases are combined, dried over potassium carbonate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The mixture is purified by distillation. 2-Diethylamino-1-propanethiol (5.8 g) is obtained in the form of a colourless liquid. [B.p. (2.7 kPa) = 78° C.]

1-S-Isothioureido-2-diethylaminopropane dihydrochloride can be prepared as follows:

Thiourea (16.7 g) is added to a solution of 1-chloro-2-diethylaminopropane hydrochloride (41 g) in dimethylformamide (200 cc). The mixture is heated to 100° C. for 30 minutes, and then cooled to 20° C. The white precipitate formed is collected by filtration, washed with dimethylformamide (3 × 20 cc) and then with ethyl ether (3 × 20 cc). 1-S-Isothioureido-2-diethylaminopropane dihydrochloride (29.6 g) is obtained in the form of white crystals melting at 247°–249° C.

1-Chloro-2-diethylaminopropane hydrochloride can be obtained as follows:

2-Diethylaminopropanol hydrochloride (45.2 g) is added over 15 minutes to thionyl chloride (100 cc) and the mixture is heated to 80° C. After 2 hours' stirring, excess thionyl chloride is distilled off and the residue is taken up with ethyl ether (200 cc). 1-Chloro-2-diethylaminopropane hydrochloride crystallizes out. After filtration, white crystals (48.2 g) melting at 112° C. are obtained.

2-Diethylaminopropanol hydrochloride can be obtained as follows:

A solution of ethyl 2-diethylaminopropionate (66 g) in ethyl ether (330 cc) is added slowly at 20° C. to a suspension of lithium aluminium hydride (10.6 g) in ethyl ether (1 liter) kept under nitrogen. The reaction is maintained for 5 hours at a temperature of 35° C., and the temperature is then lowered to 0° C. Water (12.4 cc), a 5N aqueous solution of sodium hydroxide (9.1 cc) and then water (41.3 cc) are then added dropwise at 0° C., the mixture is stirred for 30 minutes and is then filtered through sintered glass and is then washed with ethyl ether. The ether phase is dried over potassium carbonate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. A yellow liquid (43.8 g) is obtained and is dissolved in acetone

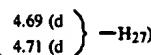
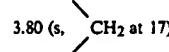
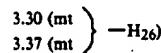
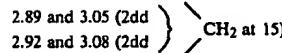
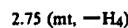
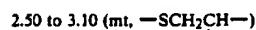
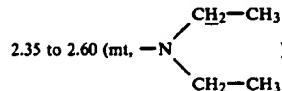
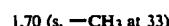
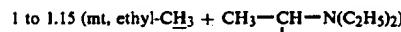
(200 cc), to which a 4.5N solution (78 cc) of hydrogen chloride gas in ethyl ether is then added. 2-Diethylaminopropanol hydrochloride crystallizes out. After filtration, white crystals (45.2 g) melting at 97°–100° C. are obtained.

Ethyl 2-diethylaminopropionate can be obtained according to Braun et al., Beilstein, 61, 1425 (1928).

EXAMPLE 8

10 The method used is similar to that described in Example 2, but starting from 26-(2-diethylaminopropyl)thiopristinamycin II_B (isomers A) (4 g), 98% metachloroperbenzoic acid (1.16 g) and solid sodium bicarbonate (1 g). After purification by "flash" chromatography [eluent: chloroform-methanol (93-7) by volume] and concentrating fractions 21 to 48 to dryness under reduced pressure (2.7 kPa) at 30° C., 25-cc fractions being collected, 26-(2-diethylaminopropyl)sulphinylpristinamycin II_B (isomers A₂) (2.69 g) is obtained in the form of a yellow powder which has characteristics identical to those of the product obtained in Example 7.
 20 26-(2-Diethylaminopropyl)thiopristinamycin II_B (isomer A) can be obtained by using a method similar to that described in Example 1, but starting from pristinamycin II_A (15 g) and 2-diethylaminopropanethiol (4.62 g). After purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 27 to 52 to dryness under reduced pressure (2.7 kPa) at 30° C., 40-cc fractions being collected, a yellow solid (12 g) is obtained and stirred in ethyl ether (60 cc), filtered off and then dried. 26-(2-Diethylaminopropyl)thiopristinamycin II_B (isomer A) (8.2 g) is obtained in the form of a light-yellow powder melting at about 122° C.

NMR spectrum:



35

-continued

5.45 (d, —H₁₃)6.13 (d } —H₁₁)
6.14 (d }

6.4 to 6.60 (mt, NH at 8)

6.51 (dd } —H₅)
6.53 (dd }8.09 (s, —H₂₀)

2-Diethylaminopropanethiol can be obtained as described earlier in Example 7.

EXAMPLE 9

The method used is similar to that described in Example 2 but starting from 26-(1-diethylamino-2-propyl)-thiopristinamycin II_B (isomers A) (4.58 g), 98% meta-chloroperbenzoic acid (1.29 g) and solid sodium bicarbonate (1.14 g). After purification by "flash" chromatography [eluent: chloroform-methanol (97-3 by volume)], 20-cc fractions being collected, and concentrating, respectively, fractions 59 to 77 and fractions 79 to 97 under reduced pressure (2.7 kPa) at 30° C., there are obtained: from fractions 79 to 97, 26-(1-diethylamino-2-propyl)sulphinylpirstinamycin II_B (first isomer) (1.47 g) in the form of a light-yellow solid melting at about 132° C.

NMR spectrum:1.02 (t, ethyl-CH₃)1.34 (d, CH₃—CH—CH₂N(C₂H₅)₂)1.72 (s, —CH₃ at 33)2.5 to 2.7 (mt, —CH₂—N
 |
 CH₂—)2.77 (mt, —H₄)2.87 and 3.09 (2dd, CH₂ at 15)2.97 (mt, —S—CH
 |
 O)3.72 (mt, —H₂₆)

3.80 (s, CH at 17)

4.92 (mt, —H₂₇)
5.43 (d, —H₁₃)
6.15 (d, —H₁₁)**36**

-continued

5 6.72 (dd, NH at 8)

8.06 (s, —H₂₀)

and from fractions 59 to 77, 26-(1-diethylamino-2-propyl)sulphinylpirstinamycin II_B (second isomer) (1.07 g) in the form of a light-yellow solid melting at about 128° C.

NMR spectrum: 1.72 (s, CH₃ at 33), 3.4 (mt, —H₂₆), 3.79 (s, CH₂ at 17), 4.74 (mt, —H₂₇), 5.48 (d, —H₁₃), 6.18 (d, —H₁₁), 6.80 (mf, >NH at 8), 8.09 (s, —H₂₀).

26-(1-Diethylamino-2-propyl)thiopristinamycin II_B (isomers A) can be obtained by using a method similar to that described in Example 1 but starting from pristinamycin II_A (13 g) and 1-diethylamino-2-propanethiol (4 g). After purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 46 to 55 to dryness under reduced pressure (2.7 kPa) at 30° C., 50-cc fractions being collected, a pale yellow solid (8 g) is obtained and recrystallized from acetonitrile (30 cc). After filtration and drying, 26-(2-diethylamino-2-propyl)thiopristinamycin II_B (isomers A) (5.91 g) is obtained in the form of white crystals melting at 136° C.

NMR spectrum:

0.9 to 1.10 (mt, —N(CH₂CH₃)₂)35 1.33 to 1.37 (2d, CH₃—CH—CH₂N)1.7 (s, —CH₃ at 33)40 2.4 to 2.65 (mt, —CH₂N
 |
 CH₂—
 |
 CH₂—)2.76 (mt, —H₄)

3 (mt, —S—CH)

50 2.9 and 3.1 (2dd, CH₂ at 15)3.52 (mt, —H₂₆)3.81 (s, CH₂ at 17)4.78 (mt, —H₂₇)5.46 (d, —H₁₃)6.14 (d, —H₁₁)

65 6.40 (mt, NH at 8)

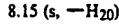
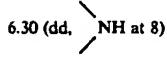
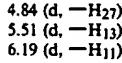
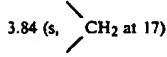
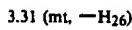
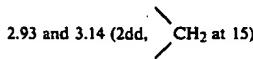
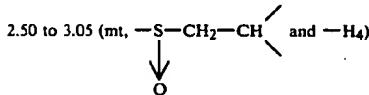
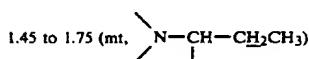
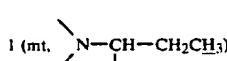
-continued
8.09 and 8.10 (2s, —H₂₀)

1-Diethylamino-2-propanethiol can be obtained according to the method described by R. T. Wragg, J. 5 Chem. Soc. (C), 2087 (1969).

EXAMPLE 10

A method similar to that described in Example 2 is used, but starting from 26-[2(R)-2-dimethylaminobutyl]-thiopristinamycin II_B (isomer A) (1.7 g), sodium bicarbonate (0.50 g) and 98% meta-chloroperbenzoic acid (0.45 g). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (85-15 by volume)] and concentrating fractions 35 to 58 to dryness under reduced pressure (2.7 kPa) at 30° C., a white solid (1.1 g) is obtained which is stirred in ethyl ether (30 cc). After filtration and drying, 26-[2(R)-2-dimethylaminobutyl]-sulphinylpristinamycin II_B (isomer A₂) (0.95 g) is obtained in the form of a white solid melting at about 126° 15 C.

NMR spectrum:

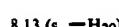
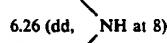
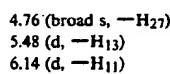
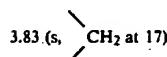
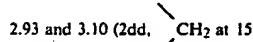
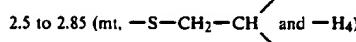
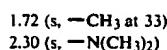
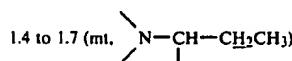
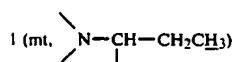


26-[2(R)-2-Dimethylaminobutyl]thiopristinamycin II_B (isomer A) can be obtained by using a method similar to that described in Example 1 but starting from pristinamycin II_A (8 g) and (2R)-2-dimethylaminobutanethiol. After purification by "flash" chromatography [eluent: dichloromethane-methanol (90-10 by volume)] and concentrating fractions 36 to 55 to dryness under reduced pressure (2.7 kPa) at 30° C., 60 65 26-[(2R)-2-dimethylaminobutyl]thiopristinamycin II_B

(isomer A) (3 g) is obtained in the form of a light-yellow solid melting at about 120° C.

Crystallization of this product (0.9 g) from acetonitrile (5 cc) produces, after separation by filtration, 26-[2(R)-2-dimethylaminobutyl]thiopristinamycin II_B (isomer A) (0.2 g) in the form of white crystals melting at 122° C.

NMR spectrum:



(R)-2-Dimethylaminobutanethiol can be obtained using a method similar to that described below in Example 11, starting from triphenylphosphine (52.4 g), diisopropyl azodicarboxylate (40 cc), (R)-2-dimethylaminobutanol (12 g) and thiolacetic acid (15.2 cc) (in this case, the intermediate thioester is hydrolysed directly during the chromatography on silica gel).

55 After purification by "flash" chromatography [eluent: dichloromethane: 1000 cc, then dichloromethane-methanol (85-15 by volume): 2000 cc, then dichloromethane-methanol (80-20 by volume): 4000 cc], 100-cc fractions being collected, and concentrating fractions 42 to 60 to dryness under reduced pressure, a yellow oil (14 g) is obtained, which is purified by distillation. In this manner, (R)-2-dimethylaminobutanethiol (2.4 g) is obtained in the form of a colourless liquid. [B.p. (4 kPa)=70°-75° C.]

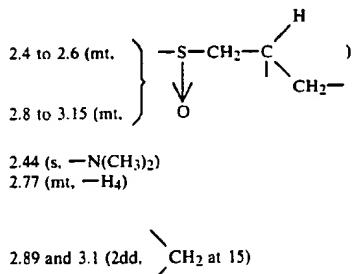
(R)-2-Dimethylamino-1-butanol can be obtained by a method identical to that described by M. Wenghoefer et al., J. Heterocycl. Chem., 7(6), 1407 (1970).

EXAMPLE 11

26-[(2S)-2-Dimethylamino-3-phenylpropyl]thiopristinamycin II_B (isomer A) (2.67 g), sodium bicarbonate (0.7 g) and 98% meta-chloroperbenzoic acid (0.7 g), after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 20-cc fractions being collected, and concentrating fractions 19 to 23 to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid (1.3 g) is obtained, which is stirred in ethyl ether (50 cc), and separated off by filtration to give 26-[(2S)-2-dimethylamino-3-phenylpropyl]sulphinylpirstinamycin II_B (isomer A₂) (1.18 g) in the form of a light-yellow solid melting at about 150° C.

NMR spectrum (400 MHz, CDCl₃)

1.73 (s, —CH₃ at 33)



An aqueous solution containing 1% of 26-[(2S)-2-dimethylamino-3-phenylpropyl]sulphinylpirstinamycin II_B (isomer A₂) is obtained with:

product	30 mg
0.1 N hydrochloric acid	0.45 cc
distilled water q.s.	3 cc

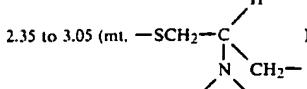
26-[(2S)-2-Dimethylamino-3-phenylpropyl]thiopristinamycin II_B (isomer A) can be prepared by using a method similar to that described in Example 1 for the preparation of the starting material, but starting from pristinamycin II_A (7.13 g) and (S)-2-dimethylamino-3-phenylpropanethiol (2.65 g) and after purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 60-cc fractions being collected, and concentrating fractions 33 to 43 to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid (4.6 g) is obtained which is stirred in ethyl

ether (50 cc), filtered off and then dried under reduced pressure (90 Pa) at 45° C. In this manner, 26-[(2S)-2-dimethylamino-3-phenylpropane]thiopristinamycin II_B (isomer A) (3.6 g) is obtained in the form of a pale yellow powder melting at about 110° C.

NMR spectrum:

1.69 (s, —CH₃ at 33)

2.38 (s, —N(CH₃)₂)



(S)-2-Dimethylamino-3-phenylpropanethiol can be prepared as follows:

Sodium methoxide (0.2 g) is added under a nitrogen atmosphere to (S)-2-dimethylamino-3-phenylpropanethiolacetate (20 g; crude) dissolved in methanol (50 cc) and the mixture is heated under reflux for 2 hours. The mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give a liquid which is purified by distillation. (S)-2-Dimethylamino-3-phenylpropanethiol (2.4 g) is obtained in the form of a colourless liquid [b.p. (14 Pa)=95° C.] which is used as such in the reaction which follows.

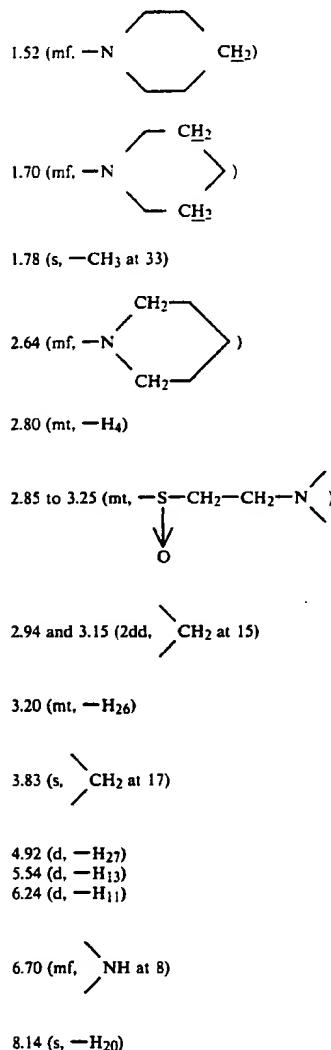
(S)-2-Dimethylamino-3-phenylpropanethiolacetate can be prepared as follows:

Triphenylphosphine (41.97 g) and tetrahydrofuran (310 cc) are added at 0° C. under a nitrogen atmosphere, and then diisopropyl azodicarboxylate (31.5 cc) is added dropwise and the mixture is left stirred for half an hour at 0° C. A mixture of (S)-2-dimethylamino-3-phenylpropanol (15 g) and of thiolacetic acid (11.44 cc) dissolved in tetrahydrofuran (160 cc) is added dropwise to the white suspension obtained. After being stirred for 1 hour at 0° C. and then for 1 hour 30 minutes at 25° C.,

43

tinamycin II_B (isomer A) (6 g), trifluoroacetic acid (0.69 cc) and 85% meta-chloroperbenzoic acid (1.82 g), after purification by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 20-cc fractions being collected and concentrating fractions 52 to 105 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (4.7 g) is obtained, which is again purified by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 5-cc fractions being collected. After concentrating fractions 92 to 99 under reduced pressure (2.7 kPa) at 30° C., a yellow solid (1.83 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration, and then dried under reduced pressure (90 Pa) at 30° C. In this manner, 26-(2-piperidinoethyl)thiopristinamycin II_B (isomers: 90% A₂, 10% A₁) (1.51 g) is obtained in the form of a yellow powder melting at about 162° C.

NMR spectrum (400 MHz, CDCl₃)



After concentrating fractions 100 to 140 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (2.11 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30° C. 26-(2-Piperidino-

44

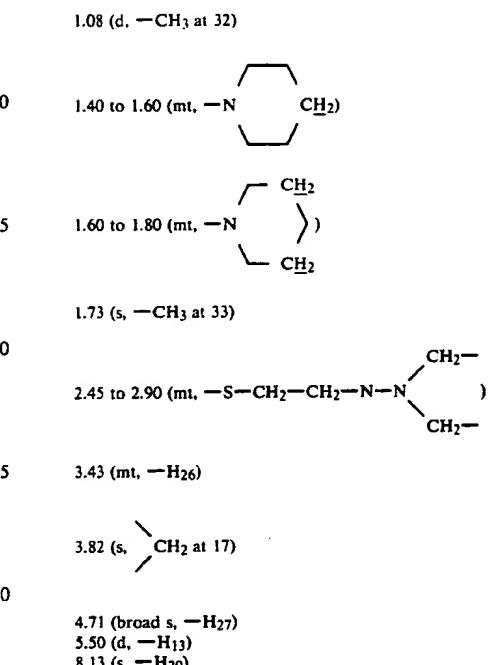
thiyl)thiopristinamycin II_B (isomers: 50% A₁, 50% A₂) (1.75 g) is obtained in the form of a yellow powder melting at about 152° C.

NMR spectrum (400 MHz, CDCl₃), 1.74 (s, —CH₃ at 33 isomer A₁), 1.78 (s, —CH₃ at 33 isomer A₂), 3.20 (mt, —H₂₆ isomer A₂), 3.46 (mt, —H₂₆ isomer A₁), 3.82 (borderline AB, >CH₂ at 17 isomer A₁), 3.83 (s, >CH₂ at 17 isomer A₂), 4.90 (d, —H₂₇ isomer A₂), 5.30 (s, —H₂₇ isomer A₁), 5.52 (d, —H₁₃ isomer A₁), 5.54 (d, —H₁₃ isomer A₂), 6.60 (dd, —H₅ isomer A₂), 6.70 (dd, —H₅ isomer A₁), 8.14 (s, —H₂₀, isomers A₂ and A₁)

26-(2-Piperidinoethyl)thiopristinamycin II_B (isomer A) can be obtained as follows:

By using a method similar to that described in Example 1, but starting from pristinamycin II_A (11.8 g) and 2-piperidinoethanethiol (3.58 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 60-cc fractions being collected, and concentrating fractions 24 to 31 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-piperidinoethyl)thiopristinamycin II_B (isomer A) (8.3 g) is obtained in the form of a light-yellow powder melting at about 120° C.

NMR spectrum:



55 2-Piperidinoethanethiol can be obtained by a method identical to that described by D. D. Reynolds, D. L. Fields and D. J. Johnson, *J. Org. Chem.*, 26, 5125 (1961).

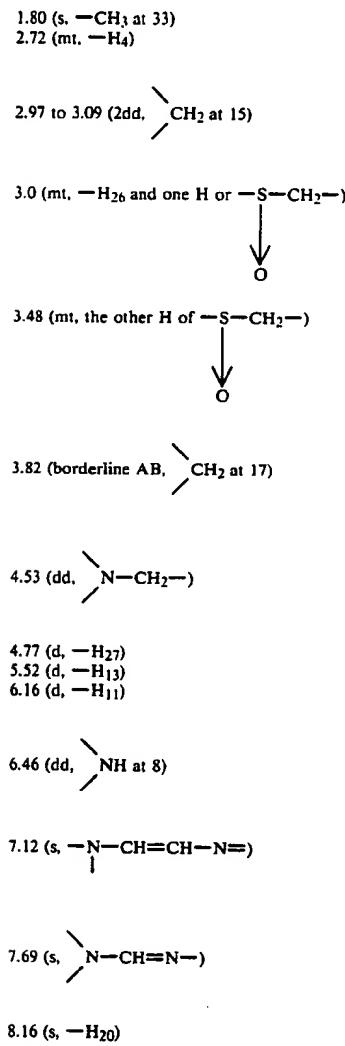
EXAMPLE 14

60 By using a method similar to that described in Example 2, but starting from 26-[2-(1-imidazolyl)ethyl]thiopristinamycin II_B (isomers: 85% A, 15% B) (3.2 g), sodium bicarbonate (1 g) and 98% meta-chloroperbenzoic acid (0.93 g), after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 25-cc fractions being collected, and concentrating fractions 29 to 49 to dryness under reduced pressure

45

(2.7 kPa) at 30° C., a yellow solid (1.4 g) is obtained. The solid obtained is purified again by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 10-cc fractions being collected. After concentrating fractions 47 to 55 to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid (0.62 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. In this manner, 26-[2-(1-imidazolyl)ethyl]sulphinylpristinamycin II_B (isomer A₂) (0.6 g) is obtained in the form of a yellow solid melting at about 170° C.

NMR spectrum (400 MHz, CDCl₃)



26-[2-(1-imidazolyl)ethyl]thiopristinamycin II_B can be prepared by using a method similar to that described in Example 3, but starting from pristinamycin II_A (14.35 g) and 2-(1-imidazolyl)ethanethiol (3.5 g), after stirring at 20° C. for 18 hours followed by purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)] and concentrating fractions 34 to 59 to dryness under reduced pressure (2.7 kPa) at 30° C.; a yellow solid is obtained, which is stirred in ethyl ether (60 cc) and then separated off by filtration, to give 26-[2-(1-imidazolyl)ethyl]thiopristina-

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mycin II_B (isomers: 85% A, 15% B) (10.9 g) in the form of a yellow solid melting at about 160° C.

NMR spectrum: 1.53 (s, —CH₃ at 33 of B), 1.73 (s, —CH₃ at 33 of A), 2.74 (mt, —H₄ of A), 2.86 and 3.14 (2 dd, >CH₂ at 15 of A), 2.85 to 3.05 (mt, —SCH₂—), 3.11 (mt, —H₂₆ of A), 3.32 (mt, —H₂₆ of B), 3.82 (borderline AB, >CH₂ at 17 of A), 4.15 to 4.30 (mt, —CH₂N>), 4.58 (d, —H₂₇ of B), 4.68 (fine d, —H₂₇ of A), 5.44 (d, —H₁₃ of A), 6.16 (d, —H₁₁ of A), 6.83 (dd, >NH at 8 of A), 6.97 and 7.08 (2s, >N—CH=CHN< of B), 7.01 and 7.10 (2s, >N—CH=CHN< of A), 7.54 (s, >N—CH=N— of B), 7.61 (s, >N—CH=N— of A), 7.64 (mt, >NH at 8 of B), 7.82 (s, —H₂₀ of B), 8.09 (s, —H₂₀ of A).

15 2-(1-Imidazolyl)ethanethiol can be prepared by a method similar to that described in Example 11 for the preparation of the starting material, but starting from 2-(1-imidazolyl)ethanethiolacetate (21 g) and sodium methoxide (0.5 g). After purification by distillation, 2-(1-imidazolyl)ethanethiol (2.3 g) is obtained in the form of an oil [b.p. (20 Pa)=99.5° C.].

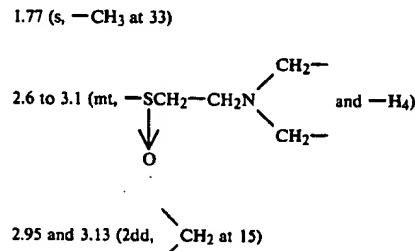
20 2-(1-Imidazolyl)ethanethiolacetate can be prepared by a method similar to that described in Example 11 for the preparation of the starting material, but starting from 2-(1-imidazolyl)ethanol (15 g), triphenylphosphine (70.2 g), diisopropyl azodicarboxylate (55.8 cc) and thiolacetic acid (21 cc). After purification by "flash" chromatography [eluent: methylene chloride (1500 cc), followed by ethyl acetate-methanol (80-20 by volume)], 100-cc fractions being collected, and concentrating fractions 21 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., 2-(1-imidazolyl)ethylthioacetate (21.14 g) is obtained in the form of an orange-yellow oil which is used without further purification.

25 2-(1-Imidazolyl)ethanol can be prepared by a method similar to that described by J. Geibel et al., J. Am. Chem. Soc., 100, 3575 (1978).

EXAMPLE 15

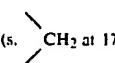
40 By using a method similar to that described in Example 2, but starting from 26-(2-morpholinoethyl)thiopristinamycin II_B (isomer A) (5.5 g), sodium bicarbonate (1.3 g), and 98% meta-chloroperbenzoic acid (1.4 g), 45 after extraction of the reaction mixture, drying of the organic phase over magnesium sulphate, filtering and concentrating to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid is obtained, which is stirred in isopropyl ether (100 cc), separated off by 50 filtration, and then dried under reduced pressure (90 Pa) at 35° C. In this manner, 26-(2-morpholinoethyl)sulphinylpristinamycin II_B (isomer A₂) (4.8 g) is obtained in the form of a light-yellow solid melting at about 126° C.

55 NMR spectrum:

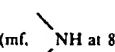


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3.20 (mt, —H₂₆)
3.78 (mt, —CH₂—O—CH₂—)

3.81 (s,  CH₂ at 17)

4.85 (mt, —H₂₇)
5.53 (d, —H₁₃)
6.20 (d, —H₁₁)

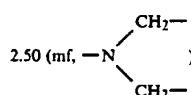
6.53 (mf,  NH at 8)

8.14 (s, —H₂₀)

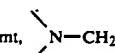
26-(2-Morpholinoethyl)thiopristinamycin II_B (isomer A) can be obtained by a method similar to that described in Example 1, but starting from pristinamycin II_A (15 g) and 2-morpholinoethanethiol (6.3 g). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (75-25 by volume)], 30-cc fractions being collected, and concentrating fractions 35 to 49 to dryness under reduced pressure (2.7 kPa) at 30° C., a beige solid (11 g) is obtained which is crystallized from acetonitrile (120 cc). In this manner, 26-(2-morpholinoethyl)thiopristinamycin II_B (isomer A) (5.7 g) is obtained in the form of white crystals melting at 132° C.

NMR spectrum:

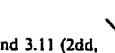
1.73 (s, —CH₃ at 33)



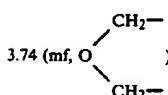
2.6 to 2.9 (mt, —H₄)

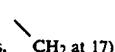
2.64 (mt,  CH₂ at 17)

2.79 (mt, —SCH₂—)

2.91 and 3.11 (2dd,  CH₂ at 15)

3.37 (broad d, —H₂₆)



3.83 (s,  CH₂ at 17)

4.74 (broad s, —H₂₇)
5.45 (d, —H₁₃)
6.13 (d, —H₁₁)

-continued

5
6.28 (mf,  NH at 8)

8.13 (s, —H₂₀)

2-Morpholinoethanethiol can be prepared by a method similar to that described by D. D. Reynolds et al., J. Org. Chem., 26, 5125 (1961).

EXAMPLE 16

By using a method similar to that described in Example 1, but starting from 26-(2-butylaminoethyl)thiopristinamycin II_B (80% isomer A, 20% isomer B) (5.8 g), trifluoroacetic acid (0.68 cc) and meta-chloroperbenzoic acid (1.8 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 15-cc fractions being collected, and concentrating fractions 9 to 15 dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)sulphinylpristinamycin II_B (70% isomer A₂, 15% isomer B₁, 15% isomer B₂) (1.7 g) is obtained in the form of a yellow powder melting at about 140° C.

NMR spectrum (isomer A₂):

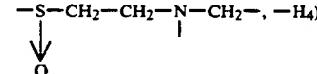
0.85 to 1.00 (mt, —CH₃ at 31 and 30 + chain —CH₃)

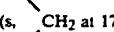
1.34 (mt, —CH₂CH₃)

1.48 (mt, —CH₂CH₂CH₂CH₃)

1.75 (s, —CH₃ at 33)

35
2.50 to 3.30 (mt, —H₂₆,  CH₂ at 2,

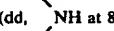


3.80 (s,  CH₂ at 17)

4.80 (d, —H₂₇)

5.50 (d, —H₁₃)

6.17 (d, —H₁₁)

6.40 (dd,  NH at 8)

8.12 (s, —H₂₀)

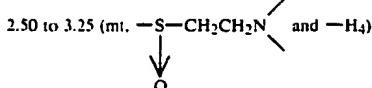
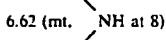
After concentrating fractions 18 to 24 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)sulphinylpristinamycin II_B (85% isomer A₁, 15% isomer B₁) (0.5 g) is obtained in the form of a yellow powder melting at about 170° C.

NMR spectrum (isomer A₁):

0.85 to 1.00 (mt, —CH₃ at 31, 30 and chain —CH₃)

1.33 (mt, —CH₂CH₃)

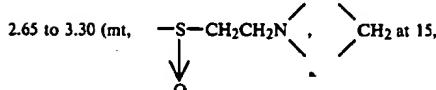
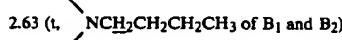
-continued

1.47 (mt. —CH₂CH₂CH₂CH₃)1.71 (s. —CH₃ at 33)3.79 (borderline AB, >CH₂ at 17)5.26 (d, —H₂₇)5.44 (d, —H₁₃)6.13 (d, —H₁₁)8.10 (s, —H₂₀)

26-(2-Butylaminoethyl)thiopristinamycin II_B (80% isomer A, 20% isomer B) can be prepared as described below in Example 17.

EXAMPLE 17

By using a method similar to that described in Example 1, but starting from 26-(2-butylaminoethyl)thiopristinamycin II_B (isomer B) (3.15 g), trifluoroacetic acid (0.37 cc) and meta-chloroperbenzoic acid (0.97 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 15-cc fractions being collected, and concentrating fractions 18 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)sulphinylpristinamycin II_B (65% isomer B₁, 35% isomer B₂) (1.18 g) is obtained in the form of a yellow powder melting at about 140° C.

NMR spectrum:0.90 to 1.05 (mt, —CH₃ at 30 and 31 andchain —CH₃ of B₁ and B₂)1.40 (mt, —CH₂CH₃ of B₁ and B₂)1.50 (mt, —CH₂CH₂CH₂CH₃ of B₁ and B₂)1.57 (s, —CH₃ at 33 of B₁ and B₂)3.74 and 3.92 (2d, >CH₂ at 17 of B₁)

-continued

5

3.73 and 3.94 (2d, >CH₂ at 17 of B₂)

10

4.78 (d, —H₂₇ of B₂)4.75 to 4.90 (mt, —H₁₃ and —H₁₄ of B₁ and B₂)5.27 (d, —H₂₇ of B₁)5.70 (2d, —H₁₁ of B₁ and B₂)7.69 (dd, >NH at 8 of B₂)

15

7.79 (dd, >NH at 8 of B₁)

20

7.84 (s, —H₂₀ of B₂)

25

7.85 (s, —H₂₀ of B₁)

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (25 g) and 2-butylaminoethanethiol (6.34 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 60-cc fractions being collected, and concentrating fractions 12 to 15 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)thiopristinamycin II_B (isomer B) (3.15 g) is obtained in the form of a yellow powder melting at about 110° C. After concentrating fractions 15 to 25 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)thiopristinamycin II_B (80% isomer A, 20% isomer B) (5.89 g) is obtained.

EXAMPLE 18

By using a method similar to that described in Example 1, but starting from 26-(2-decyldaminoethyl)thiopristinamycin II_B (8.6 g), trifluoroacetic acid (0.9 cc) and meta-chloroperbenzoic acid (2.35 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 12 to 15 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decyldaminoethyl)sulphinylpristinamycin II_B (80% isomer A₂) (1.5 g) is obtained in the form of a yellow powder melting at about 128° C.

NMR spectrum: 0.88 (t, —(CH₂)₉—CH₃), 1.30 ([m, (>CH₂)₈], 1.50 [m(>CH₂)₈], 1.77 (s, —CH₃ at 33), 4.81 (d, —H₂₇), 5.51 (d, —H₁₃), 6.19 (d, —H₁₁), 6.53 (mt, >NH at 8), 8.13 (s, —H₂₀).

After concentrating fractions 15 to 19 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decyldaminoethyl)sulphinylpristinamycin II_B (mixture of isomers) (2.51 g) is obtained in the form of a yellow powder melting at about 124° C.

NMR spectrum (mixture of isomers: 50% type A₂, 15% A₁, 20% B₁ and 15% B₂), 1.54 (s, —CH₃ at 33 of B₁ and B₂), 3.72 and 3.88 (2 d, >CH₂ at 17 of B₁), 3.70 and 3.92 (2d, >CH₂ at 17 of B₂), 4.75 (d, —H₂₇ of B₂), 5.25 (d, —H₂₇ of B₁), 7.67 (dd, >NH at 8 of B₂), 7.77 (dd, >NH at 8 of B₁), 7.81 (s, —H₂₀ of B₁ and B₂),

(characteristic peaks of isomers A₂ and A₁, identical to those mentioned above and below, respectively).

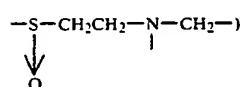
An aqueous solution containing 1% of 26-(2-decylaminoethyl)sulphinylpristinamycin II_B in the form of hydrochloride is obtained with:

26-(2-decylaminoethyl)sulphinylpristinamycin II _B	15 mg
0.1 N hydrochloric acid	0.2 cc
distilled water q.s.	1.5 cc.

After concentrating fractions 20 to 24 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decylaminoethyl)sulphinylpristinamycin II_B (isomers: 60% A₁, 20% A₂, 20% B₁) (1.12 g) is obtained in the form of a yellow powder melting at about 136° C.

NMR spectrum (isomer A₁):

2.50 to 3.20 (mt, CH₂ at 15, —H₄ and



3.82 (borderline AB, CH₂ at 17)

5.27 (d, —H₂₇)
5.46 (d, —H₁₃)
6.15 (d, —H₁₁)

6.62 (mt, NH at 8)

8.12 (s, —H₂₀)

26-(2-Decylaminoethyl)thiopristinamycin II_B can be prepared as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (5.25 g) and 2-decylaminoethanethiol (3.26 g), and after purification by "flash" chromatography [eluent: methylene chloride-methanol (95-5 by volume)], and concentrating fractions 20 to 43 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decylaminoethyl)thiopristinamycin II_B (1.2 g) is obtained in the form of a yellow powder melting at about 80° C.

NMR spectrum (70-30 mixture of A and B isomers):

0.88 (t, —CH₃)

1.30 } (mt, —(CH₂)₈—)
1.53 }

1.54 (s, —CH₃ at 33 of B)
1.72 (s, —CH₃ at 33 of A)

2.6 to 3 (mt, —SCH₂—CH₂—N—CH₂—)

3.38 (broad d, —H₂₆ of A)
3.50 (mt, —H₂₆ of B)
4.64 (d, J = 3.5, —H₂₇ of B)
4.72 (broad s, —H₂₇ of A)

-continued

7.80 (s, —H₂₀ of B)
8.12 (s, —H₂₀ of A)

EXAMPLE 19

By using a method similar to that described in Example 1, starting from 26-(2-cyclohexylaminoethyl)sulphinylpristinamycin II_B (isomers: 80% A, 20% B) (4.4 g), trifluoroacetic acid (0.5 cc) and meta-chloroperbenzoic acid (1.15 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 24 to 29 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-cyclohexylaminoethyl)sulphinylpristinamycin II_B (90% isomer A₂) (0.38 g) is obtained in the form of a light-yellow powder melting at about 166° C.

NMR spectrum:

1.05 to 1.35 [mt, cyclohexyl CH₂ (partly)]

1.77 (s, —CH₃ at 33)

1.55 to 2.25 [mt, CH₂ at 25, —H₂₉ and

cyclohexyl CH₂ (partly)]

2.45 to 3.35 (mt, —H₂₆, CH₂ at 15, —H₄ and

—S—CH₂CH₂N—CH₂—)

3.82 (s, CH₂ at 17)

4.82 (d, —H₂₇)
5.52 (d, —H₁₃)
6.19 (d, —H₁₁)

6.38 (dd, NH at 8)

8.14 (s, —H₂₀)

26-(2-Cyclohexylaminoethyl)thiopristinamycin II_B can be obtained as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (5.25 g) and 2-cyclohexylaminoethanethiol (3.6 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (93-7 by volume)] and concentrating fractions 7 to 18 to dryness under reduced pressure (2.7 kPa) at

30° C., 26-(2-cyclohexylaminoethyl)thiopristinamycin II_B (1.7 g) is obtained in the form of a beige powder melting at about 120° C.

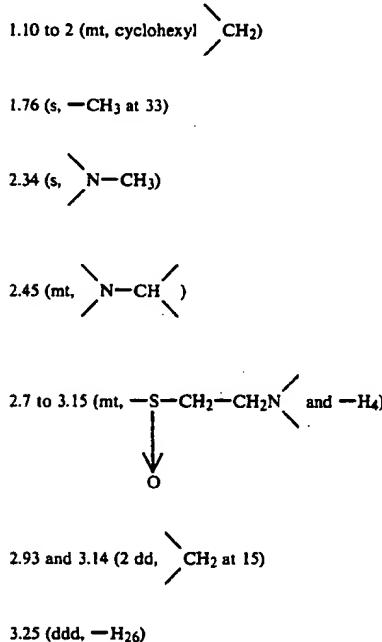
NMR spectrum: 1 to 1.4 [mt, cyclohexyl >CH₂ (partly)], 1.54 (s, —CH₃ at 33 isomer B), 1.73 (s, —CH₃) at 33 isomer A), 1.6 to 2 [mt, cyclohexyl >CH₂ (partly)], 2.80 (mt, >NCH₂—), 2.93 (t, —SCH₂—), 3.36 (broad d, —H₂₆ isomer A), 3.50 (mt, —H₂₆ isomer B), 4.64 (d, J=3, —H₂₇ isomer B), 4.72 (broad s, —H₂₇ isomer A), 6.50 (mt, —NH₃ isomer A), 7.75 (mt, —NH₃ isomer B), 7.80 (s, —H₂₀ isomer B), 8.12 (s, —H₂₀ isomer A).

2-Cyclohexylaminoethanethiol can be prepared according to the method described by D. D. Reynolds, M. K. Massad, D. L. Fields and D. L. Johnson, J. Org. Chem. 26, 5109 (1961).

EXAMPLE 20

By using a method similar to that described in Example 2, but starting from 26-(N-cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin II_B (isomers: 80% A, 20% B) (5 g), sodium bicarbonate (1.17 g) and 98% metachloroperbenzoic acid (1.2 g), after purification by "flash" chromatography [eluent: dichloromethane-methanol (80-20 by volume)], 30-cc fractions being collected, and concentrating fractions 40 to 60 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (3.5 g) is obtained, which is purified again by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 25-cc fractions being collected. After concentrating fractions 11 to 18 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (1.2 g) is obtained, which is stirred in ethyl ether (30 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 35° C. In this manner, 26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphinyliopristinamycin II_B (isomer A₂) (1.1 g) is obtained in the form of a yellow powder melting at about 126° C.

NMR spectrum:



-continued

3.82 (s, >CH₂ at 17)

4.82 (d, —H₂₇)
5.52 (d, —H₁₃)
6.18 (d, —H₁₁)

6.43 (dd, <NH at 8)

8.13 (s, —H₂₀)

26)-(N-Cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin II_B (isomers: 80% A, 20% B) can be obtained by a method similar to that described in Example 3 for the preparation of the starting material, but starting from pristinamycin II_A (10.5 g) and N-cyclohexyl-N-methyl-2-aminoethanethiol (4 g). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 30-cc fractions being collected, and concentrating fractions 42 to 96 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid is obtained which is stirred in isopropyl ether (80 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 35° C. In this manner, 26-(N-cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin II_B (isomers: 80% A and 20% B) (7.9 g) is obtained in the form of a yellow powder melting at about 116° C.

NMR spectrum (80/20 mixture of two isomers A and B): 1.25 and 1.6 to 1.9 (mt, cyclohexyl >CH₂ for A and B), 1.56 (s, —CH₃ at 33 of B), 1.73 (s, —CH₃ at 33 of A), 2.25 to 2.5 (mt, cyclohexyl >CH— for A and B), 2.32 (s, >N—CH₃ of B), 2.35 (s, >N—CH₃ of A), 2.6 to 2.8 (mt, —H₄ of A and B), 2.78 (borderline AB, —SCH₂CH₂N< of A and B), 2.9 and 3.14 (2dd, >CH₂ at 15 of A), 3.41 (broad d, —H₂₆ of A), 3.73 and 3.91 (2d, >CH₂ at 17 of B), 3.83 (s, >CH₂ at 17 of A), 4.65 (d, —H₂₇ of B), 4.76 (broad s, —H₂₇ of A), 5.49 (d, —H₁₃ of A), 6.16 (d, —H₁₁ of A), 6.36 (mf, >NH at 8 of A), 7.73 (mf, >NH at 8 of B), 7.82 (s, —H₂₀ of B), 8.13 (s, —H₂₀ of A).

N-Cyclohexyl-N-methyl-2-aminoethanethiol can be obtained as follows:

A 6N aqueous solution of sodium hydroxide (23 cc) is added under a nitrogen atmosphere to S-(N-cyclohexyl-N-methyl-2-aminoethyl)isothiouronium dihydrochloride (20 g). After being stirred at 100° C. for 2 hours, the mixture is cooled to 25° C. and then a concentrated solution of hydrochloric acid is added to it to a pH of 9. The solution is washed with dichloromethane (3×50 cc) and then the organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give an oil, which is purified by distillation under reduced pressure (130 Pa). N-Cyclohexyl-N-methyl-2-aminoethanethiol (4.3 g) is obtained in the form of a colourless liquid [b.p. (130 Pa) = 68° C.]

N-Cyclohexyl-N-methyl-2-aminoethanethiouronium dihydrochloride can be obtained as follows:

Thiourea (10.7 g) is added to 2-(N-cyclohexyl-N-methyl-amino)-1-chloroethane hydrochloride (30 g) in ethanol (300 cc). The solution obtained is heated for 18 hours at 78° C. After cooling, the white solid obtained is filtered off and then washed with ethanol. In this

55

manner, N-cyclohexyl-N-methyl-2-aminoethanethiouronium dihydrochloride (21.5 g) is obtained in the form of a white solid melting at 248° C.

2-(N-Cyclohexyl-N-methyl-amino)-1-chloroethane hydrochloride can be obtained as follows:

N-Cyclohexyl-N-methyl-2-aminoethanol (25 g) is added dropwise to thionyl chloride (120 cc) and then the mixture is heated for 24 hours at 70° C. After the excess thionyl chloride has been distilled off, the orange oil obtained is stirred into ethyl ether (200 cc) to give a white solid, which is separated off by filtration and then washed with ether. 2-(N-Cyclohexyl-N-methyl-amino)-1-chloroethane (30 g) is obtained in the form of a white solid melting at 154° C.

EXAMPLE 21

By using a method similar to that described in Example 1, but starting from 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]thiopristinamycin II_B (isomer A) (4.3 g) trifluoroacetic acid (0.45 cc) and meta-chloroperbenzoic acid (1.2 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 30-cc fractions being collected, and concentrating fractions 42 to 56 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]sulphinylpristinamycin II_B (isomer A₂) (1.2 g) is obtained in the form of a light-yellow powder melting at about 135° C.

NMR spectrum:

1.78 (s, —CH₃ at 33)

2.32 (s,

2.42 (m, —CO—N

2.95 to 3.28 (2mt, —S—CH₂—)

3.54 (m, —CO—N

3.82 (s,

4.58 (mt, —CH₂—O—C(=O)—N 4.82 (d, —H₂₇)
5.50 (d, —H₁₃)
6.20 (d, —H₁₁)

6.39 (dd,

56

-continued

8.14 (s, —H₂₀)

After concentrating fractions 65 to 95 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]sulphinylpristinamycin II_B (isomer A₁) (0.65 g) is obtained in the form of a light-yellow powder melting at about 140° C.

NMR spectrum:

1.75 (s, —CH₃ at 33)

2.34 (s,

2.44 (m, —CO—N

2.90 to 3.15 (mt, —S—CH₂—)

3.55 (m, —CO—N

3.83 (s,

4.51 to 4.65 (2ddd, —CH₂—O—C(=O)—N 5.28 (d, —H₂₇)6.19 (d, —H₁₁)

6.55 (dd,

8.14 (s, —H₂₀)

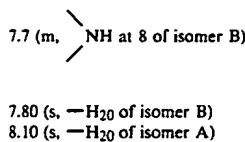
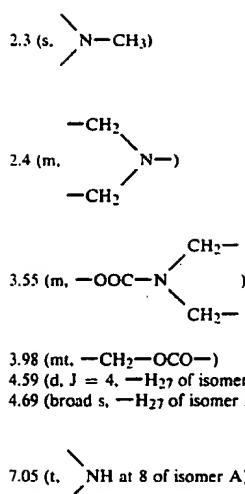
26-[(4-Methyl-1-piperazinyl)-2-carbonyloxyethyl]thiopristinamycin II_B can be prepared as follows:

By using a method similar to that described in Example 3, starting from pristinamycin II_A (5.25 g) and (4-methyl-1-piperazinyl)-2-carbonyloxyethanethiol (3.76 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 10 to 18 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]thiopristinamycin II_B is obtained in the form of a beige powder melting at about 100° C.

NMR spectrum:

1.54 (s, —CH₃ at 33 of isomer B)1.73 (s, —CH₃ at 33 of isomer A)

-continued

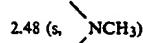


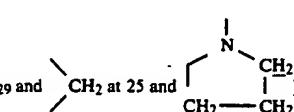
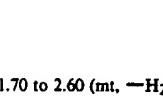
(4-Methyl-1-piperazinyl)-2-carbonyloxyethanethiol can be prepared according to the method described by D. D. Reynolds, D. L. Fields and D. L. Johnson, J. Org. Chem. 26, 5111 (1961).

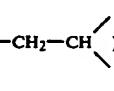
EXAMPLE 22

By using a method similar to that described in Example 1, but starting from 26-[*(S*)-1-methyl-2-pyrrolidinyl]methylthiopristinamycin II_B (isomer A) (7.8 g), trifluoroacetic acid (0.91 cc) and meta-chloroperbenzoic acid (2.4 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 60-cc fractions being collected, and concentrating fractions 26 to 36 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[*(S*)-1-methyl-2-pyrrolidinyl]methylsulphinylpristinamycin II_B (isomer A₂) (2.3 g) is obtained in the form of a light-yellow powder melting at about 140° C.

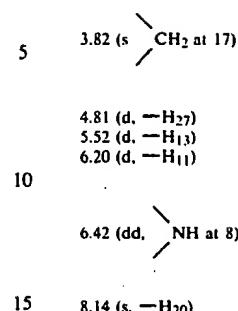
NMR spectrum:

1.76 (s, —CH₃ at 33)2.48 (s,  NCH₃)

1.70 to 2.60 (mt, —H₂₉ and  CH₂ at 25 and  CH₂—CH₂—)

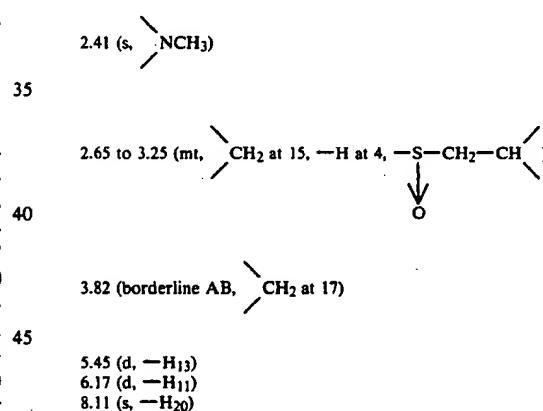
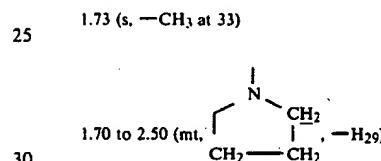
2.75 to 3.25 (mt, —S—CH₂—CH )

-continued



After concentrating fractions 46 to 59 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[*(S*)-1-methyl-2-pyrrolidinyl]methylsulphinylpristinamycin II_B (isomer A₁) (1.1 g) is obtained in the form of a light-yellow powder melting at about 148° C.

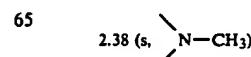
NMR spectrum:



55 26-(1-Methyl-2-pyrrolidinyl)methylthiopristinamycin II_B can be prepared as follows:

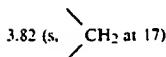
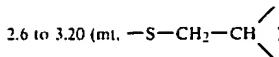
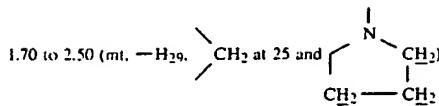
By using a method similar to that described in Example 3, but starting from pristinamycin II_A (10.5 g) and [*(S*)-1-methyl-2-pyrrolidinyl]methanethiol (3.14 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 20 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., the A isomer (7.8 g) is obtained in the form of a yellow powder melting at approximately 120° C.

NMR spectrum:

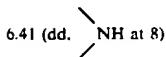
1.70 (s, —CH₃ at 33)

59

-continued



4.73 (d. —H₂₇)
5.45 (d. —H₁₃)
6.15 (d. —H₁₁)



8.11 (s. —H₂₀)

A 4N aqueous solution of sodium hydroxide (100 cc) is added to crude S-[*(S*)-1-methyl-2-pyrrolidinylmethyl]isothiouronium dihydrochloride (25 g) dissolved in distilled water (100 cc), and then the mixture is stirred for 2 hours at 90° C. under a nitrogen atmosphere. The reaction mixture is cooled to 0° C., a 12N aqueous solution of hydrochloric acid (25 cc) is added to it, and then it is extracted with methylene chloride (2 × 200 cc). The organic phase is dried over sodium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner [*(S*)-1-methyl-2-pyrrolidinyl]methanethiol (5.9 g) is obtained in the form of a light-yellow oil, which is used in the subsequent reaction without additional purification.

R_f=0.15; silica gel chromatographic plate; eluent: chloroform-methanol (90-10 by volume).

Thiourea (10.7 g) is added to [*(S*)-1-methyl-2-pyrrolidinyl]chloromethane hydrochloride (11.9 g) dissolved in ethanol (50 cc), and then the mixture is stirred for 48 hours under reflux. The mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. The residue is taken up again with hot ethanol (100 cc) and then filtered through activated plant charcoal. After the filtrate has been concentrated to dryness under reduced pressure (2.7 kPa) at 40° C., a light-yellow oil (25 g) consisting of S-[*(S*)-1-methyl-2-pyrrolidinylmethyl]isothiouronium dihydrochloride and excess thiourea, is obtained.

R_f=0.1; silica gel chromatographic plate; eluent: chloroform-methanol (90-10 by volume).

[*(S*)-1-Methyl-2-pyrrolidinyl]chloromethane hydrochloride can be prepared according to the method described by T. Hayashi et al., J. Org. Chem., 48, 2195 (1983).

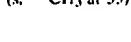
EXAMPLE 23

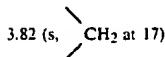
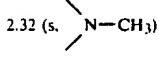
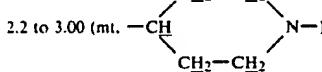
By using a method similar to that described in Example 1, but starting from 26-(1-methyl-4-piperidinyl)-thiopristinamycin II_B (2.6 g), trifluoroacetic acid (0.3 cc) and meta-chloroperbenzoic acid (0.8 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 20 to 35 to dry-

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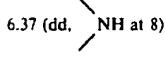
ness under reduced pressure (2.7 kPa) at 30° C., 26-(1-methyl-4-piperidinyl)sulphinylpristinamycin II_B (isomer A₂) (0.33 g) is obtained in the form of a yellow powder melting at about 170° C.

NMR spectrum:

1.76 (s. —CH₃ at 33) 



4.85 (d. —H₂₇)
5.50 (d. —H₁₃)
6.19 (d. —H₁₁)

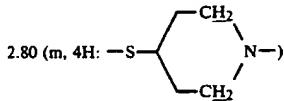
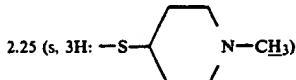
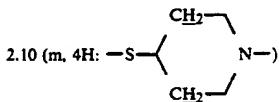


8.15 (s. —H₂₀)

26-(1-Methyl-4-piperidinyl)thiopristinamycin II_B can be obtained as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin II_A (3.15 g) and 2-methyl-4-piperidinethiol (1.6 g), and adding triethylamine (0.6 g) to the reaction mixture, and after purification by "flash" chromatography [eluent: methylene chloride-methanol (92-8 by volume)], and concentrating fractions 4 to 20 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(1-methyl-4-piperidinyl)thiopristinamycin II_B (0.9 g) is obtained in the form of a yellow powder melting at about 180° C.

NMR spectrum:



3.55 (m, 1H: —H₂₆)
4.62 (m, 1H: —H₂₇)
7.70 (m, 1H: —H₈)
8.10 (s, 1H: —H₂₀)

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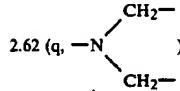
2-Methyl-4-piperidinethiol can be prepared by the method described by H. Barrer and R. E. Lyle, J. Org. Chem., 27, 641 (1962).

EXAMPLE 24

Trifluoroacetic acid (0.92 cc) is added under a nitrogen atmosphere to 26-(2-diethylaminoethyl)thiopristinamycin II_B (7.8 g) dissolved in methanol (60 cc), at 0° C. After 15 minutes at 0° C., the temperature is raised to 15° C., and then selenium dioxide (1.37 g) is added. When all the selenium dioxide has dissolved, a 30% strength aqueous solution of hydrogen peroxide (7 cc) is added slowly at a temperature below 25° C. After being stirred at 25° C. for 1 hour, the reaction mixture is cooled to 10° C., a saturated aqueous solution of sodium bicarbonate (50 cc) is added to it, and then it is extracted with methylene chloride (4×50 cc). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The yellow solid obtained is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected. After concentrating fractions 31 to 38 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid is obtained, which is purified by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 40-cc fractions being collected. After concentrating fractions 27 to 33 to dryness under reduced pressure, a white solid is obtained, which is stirred in ethyl ether (50 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30° C. In this manner, 26-(2-diethylaminoethyl)sulphonylpirstinamycin II_B (isomer A) (0.5 g) is obtained in the form of a white solid melting at about 150° C.

NMR spectrum:

0.97 (d, —CH₃ at 30 and 31 and ethyl —CH₃)
1.75 (s, —CH₃ at 33)

3.00 to 3.40 (mt, —SO₂CH₂CH₂N—)3.82 (s, CH₂ at 17)

5.34 (d, —H₁₃)
5.43 (d, —H₁₃)
6.16 (d, —H₁₁)

6.54 (dd, NH at 8)

8.10 (s, —H₂₀)

EXAMPLE 25

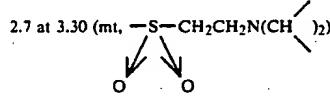
A method similar to that described in Example 24 is used, but starting from 26-(2-diisopropylaminoethyl)thiopristinamycin II_B (isomer A) (6.86 g), trifluoroacetic acid (0.77 cc), selenium dioxide (1.15 g), and a 30% strength aqueous solution of hydrogen peroxide (6.33

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cc). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 40-cc fractions being collected, and concentrating fractions 28 to 31 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (0.7 g) is obtained, which is purified again by "flash" chromatography [eluent: ethyl acetate-methanol (85-15 by volume)], 30-cc fractions being collected. After concentrating fractions 26 to 33 to dryness under reduced pressure, a yellow solid is obtained, which is stirred in ethyl ether (30 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30° C. 26-(2-Diisopropylaminoethyl)sulphonylpirstinamycin II_B (isomer A) (0.6 g) is obtained in the form of a light-yellow solid melting at about 140° C.

NMR spectrum:

1.06 (d, isopropyl —CH₃)
1.75 (s, —CH₃ at 33)
2.79 (mt, —H₄)

2.92 and 3.10 (2dd, CH₂ at 15)3.52 (broad d, —H₂₆)3.82 (s, CH₂ at 17)

5.27 (fine d, —H₂₇)
5.47 (d, —H₁₃)
6.17 (d, —H₁₁)

6.42 (mt, NH at 8)

8.12 (s, —H₂₀)

Reference Example 1

Pristinamycin I_A (0.5 g) and sodium cyanoborohydride (20 mg) are added to a solution of 3-dimethylaminopropylamine (0.41 cc) in methanol (15 cc) containing a 2N methanolic solution (2.4 cc) of hydrogen chloride gas, maintained at 55° C. The solution obtained is then allowed to regain a temperature of about 20° C. over approximately 2 hours, and it is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is triturated with a mixture of methylene chloride (50 cc) and of a saturated aqueous solution of sodium bicarbonate (50 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (20 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (80-20 by volume)]. Fractions 15 to 30 are combined and concentrated to dryness

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under reduced pressure (2.7 kPa) at 30° C.; the residue obtained is triturated with ethyl ether (5 cc), filtered off and dried under reduced pressure (0.027 kPa) at 20° C. In this manner 5γ-deoxy(3-dimethylaminopropyl)-5γ-aminopristinamycin I₄ (60 mg) is obtained in the form of a cream-colored powder melting at about 160° C.

The complete NMR spectrum shows the following characteristics:

δ (ppm)	Form of signal	Attribution
8.40	d	6 NH
8.25	d	1 NH
7.55	dd	H _b

5

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mycin I₄ (product A), in the form of hydrochloride, is obtained with:

product A	0.1 g
2 N hydrochloric acid	0.52 cc
distilled water q.s.	1 cc

By using a method similar to that described in the reference Example 1, the following synergistins of general formula (V), which can be combined with the products according to the invention, are prepared: [The symbols , Z and R₁ are defined as at (1) for the general formula (V)].

Reference example	Y	X	(1) Melting point (2) Solubility
2	—N(CH ₃) ₂	—NH(CH ₂) ₂ N(CH ₃) ₂	(1) Yellow powder M. abt 180° C. (2) 10% aqueous solution of hydrochloride
3	—N(CH ₃) ₂		(1) White powder M. abt. 195° C. (2) 10% aqueous solution of hydrochloride
4	—N(CH ₃) ₂		(1) Beige powder (2) M. abt. 195° C. 3.7% aqueous solution of hydrochloride
5	—N(CH ₃) ₂	—NHOH	(1) White powder M. abt. 170° C. (2) 10% aqueous solution of hydrochloride
6	—N(CH ₃) ₂	—NH(CH ₂) ₃ OH	(1) Cream powder M. abt. 160° C. (2) 2% aqueous solution of hydrochloride
7	—H	—NH(CH ₂) ₃ N(CH ₃) ₂	(1) Beige powder M. abt. 140° C. (2) 10% aqueous solution of hydrochloride

7.05	m	6γ + 6δ + 6ε
7	dd	H ₄
6.90	dd	H ₅
6.70	d	
		4δ + 4ε
6.40	d	2 NH
6.50	d	1β
5.75	ddd	6α
5.45	d	4α
5.25	dd	5α
5	s (broad)	5β
4.75	dd	1α
4.60	m	2α
4.45	(d broad)	5ε ₁
4.40	dd	3α
3.4	(dd broad)	3δ ₁
3.20	(dd broad)	3δ ₂
3	s	4 CH ₃
3	m	5γ + 4β ₁ and 2
2.80	s	4 N(CH ₃) ₂
2.65	t	—NCH ₂ — (chain)
2.35	m	5ε ₂ + 5β ₁
2.25	t	—NCH ₂ — (chain)
2.20	s	—N(CH ₃) ₂ (chain)
1.60	m	—CH ₂ — (chain) 2β + 3γ
1.25	d	1γ
0.90	t	2γ
0.50	dddd,	5β ₂

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Reference Example 8

A 5N ethanolic solution (2.8 cc) of dimethylamine, followed by a 5N methanolic solution (2 cc) of hydrogen chloride gas are added to a solution of pristinamycin I₄ (2 g) in methanol (25 cc). Sodium cyanoborohydride (76 mg) are added to the solution thus obtained, and the mixture is then stirred at a temperature of about 20° C. for 48 hours. The reaction mixture is then concentrated to dryness under reduced pressure (2.7 pKa) at 30° C. The residue is triturated with a mixture of methylene chloride (25 cc) and of a saturated aqueous solution of sodium bicarbonate (25 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (92-8 by volume)]. Fractions 5 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner 5γ-deoxy-5γ-dimethylaminopristinamycin I₄ (0.7 g) is obtained in the form of a beige powder melting at about 170° C.

An aqueous solution at a concentration of 10% of 5γ-deoxy-(3-dimethylaminopropyl)-5γ-amino-pristina-

NMR spectrum: 0.70 (dt, 1H: $5\beta_2$), 2.10 to 2.60 (m, 4H: $5\delta_1 + 5\delta_2 + 5\beta_1 + 5\gamma$) 2.15 (s, $3H \times 0.8$: $-N(CH_3)_2$ 1st isomer), 2.20 (s, $3H \times 0.2$: $-N(CH_3)_2$ 2nd isomer).

An aqueous solution at a concentration of 2% of 5γ -deoxy- 5γ -dimethylaminopristinamycin I₄ (product 5 B), in the form of hydrochloride, is obtained with:

product B	0.05 g
0.1 N hydrochloric acid	0.56 cc
distilled water q.s.	2.5 cc

Reference Example 9

By using a method similar to that described in reference Example 8, 5γ -deoxy- 5γ -methylaminopristinamycin I₄ (0.35 g) is obtained in the form of a yellow powder melting at about 185° C.

An aqueous solution at a concentration of 1% of 5γ -deoxy- 5γ -methylaminopristinamycin I₄, in the form 20 of hydrochloride, is obtained.

Reference Example 10

By using a method similar to that described in reference Example 8, 5γ -deoxy- 5γ -[N-(2-dimethylaminoethyl)-N-methylamino]pristinamycin I₄ is obtained in the form of a white powder melting at about 120° C.

An aqueous solution at a concentration of 10% of 5γ -deoxy- 5γ -[N-(2-dimethylaminoethyl)-N-methylamino]pristinamycin I₄ (product D), in the form 30 of hydrochloride, is obtained.

Reference Example 11

A 3-Å molecular sieve (5 g) is added to a solution of pristinamycin I₄ (3 g), 4-diethylamino-2-methylbutylamine (3.3 g), sodium cyanoborohydride (0.11 g) and a 5N methanolic solution (9 cc) of hydrogen chloride gas in methanol (75 cc). The suspension obtained is stirred at a temperature of about 20° C. for 4 days, and is then filtered; the filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is triturated with a mixture of methylene chloride (50 cc) and a saturated aqueous solution of sodium bicarbonate (50 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]. In this manner, 5γ -deoxy-15 5γ -(4-diethylamino-2-methylbutyl)aminopristinamycin I₄ (0.7 g) is obtained in the form of a beige powder melting at about 160° C.

NMR spectrum:

1.10 (mt, 9H: $-N(CH_2CH_3)_2 + -CH-\underline{CH_3}$)

ca 1.7 (m, 4H: $-CH_2-CH_2-CH_2-N(C_2H_5)_2$)
2.90 (m, 6H: $-CH_2N(CH_2CH_3)_2$)
7.70 (mt, 1H \times 0.45: 1'H₆ 1st isomer)
7.77 (mt, 1H \times 0.55: 1'H₆ 2nd isomer)

An aqueous solution at a concentration of 10% of 65 5γ -deoxy- 5γ -(4-diethylamino-2-methylbutyl)aminopristinamycin I₄ (product F) in the form of hydrochloride, is obtained with:

product F	0.1 g
0.1 N hydrochloric acid q.s.	1 cc

Reference Example 12

Sodium cyanoborohydride (0.7 g) is added to a solution of 5γ -deoxy- 5γ -hydroxyiminopristinamycin I₄ (12.5 g) in methanol (300 cc) containing a 2N methanolic solution (10 cc) of hydrogen chloride gas. The solution obtained is stirred at a temperature of about 20° C. for 2 days, and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is triturated in a mixture of methylene chloride (200 cc) and a saturated aqueous solution of sodium bicarbonate (100 cc); the organic phase is separated off and the aqueous phase is extracted with methylene chloride (100 cc). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. After purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], 5γ -deoxy- 5γ -hydroxyiminopristinamycin I₄ (6.8 g) is obtained in the form of a white powder melting at about 170° C.

NMR spectrum: 0.4 (m, 1H: $5\beta_2$), 2.45 (d, 1H: $5\beta_1$), 3.1 (d: 5γ in complex unresolved bands), 7.80 (mt, 1H \times 0.75: 1'H₆ 1st isomer), 7.95 (mt, 1H \times 0.25: 1'H₆ 2nd isomer).

5γ -Deoxy- 5γ -hydroxyiminopristinamycin I₄ can be obtained by stirring pristinamycin I₄ (15 g) and hydroxylamine hydrochloride (7.5 g) dissolved in methanol (150 cc) containing a 2N methanolic solution (8 cc) of hydrogen chloride gas for 5 hours at a temperature of about 20° C. The reaction mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is triturated with a mixture of chloroform (100 cc) and of a saturated aqueous solution of sodium bicarbonate (100 cc); the organic phase is separated off and the aqueous phase is extracted twice with chloroform (200 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, 5γ -deoxy- 5γ -hydroxyiminopristinamycin I₄ (14 g) is obtained in the form of a beige powder melting at 210° C.

NMR spectrum: 0.35 (dd, 1H: $5\beta_2$), 3.25 (m, 2H: $4\epsilon_2 + 5\beta_1$), 5.05 (d, 1H: 5α), 5.5 (m, 2H including $5\epsilon_1$), 7.80 (dd, 1H \times 0.40: 1'H₆ 1st isomer), 7.90 (dd, 1H \times 0.60: 1'H₆ 2nd isomer).

Reference Example 13

By using a method similar to that described in reference Example 11, 5γ -[N-(carboxymethyl)methylamino]- 5γ -deoxypristinamycin I₄ (0.8 g) is obtained in the form of a cream-coloured powder melting at 60 about 140° C.

An aqueous solution at a concentration of 2% of 5γ -[N-(carboxymethyl)methylamino]- 5γ -deoxypristinamycin I₄ (product K) is obtained with:

product K	0.2 g
distilled water q.s.	10 cc

Reference Example 14

Acetyl chloride (0.3 cc) is added to a solution of 5 γ -deoxy-5 γ -(2-dimethylaminoethyl)aminopristinamycin I_A (3.2 g) in chloroform (50 cc) containing triethylamine (0.6 cc). The reaction mixture is stirred at a temperature of about 20° C. for 30 minutes and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]; by concentrating fractions 10 to 21 to dryness under reduced pressure (2.7 kPa) at 30° C., 5 γ -deoxy-5 γ -[N-(2-dimethylaminoethyl)acetamido]pristinamycin I_A (1.8 g) is obtained in the form of a white powder melting at about 170° C.

NMR spectrum: 0.9 (m, 4H: 2 γ +5 β_2), 2.05 to 2.15 (m, 3H: 5 δ_1 +5 δ_2 +5 γ), 2.15 (S, 3H: -COCH₃), 2.45 (s, 6H: -N(CH₃)₂), 2.35 to 2.60 (m, 5H: >N-CH₂-CH₂-N<+5 β_1), 7.8 (mt, 1H×0.75: 1'H₆ 1st isomer), 8.25 (mt, 1H×0.25: 1'H₆ 2nd isomer).

An aqueous solution at a concentration of 10% of 5 γ -deoxy-5 γ -[N-(2-dimethylaminoethyl)acetamido]pristinamycin I_A (product L), in the form of hydrochloride, is obtained with:

product L	0.1 g
0.2 N hydrochloric acid	0.51 cc
distilled water q.s.	1 cc

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5 γ -Deoxy-5 γ -(2-dimethylaminoethyl)aminopristinamycin I_A can be prepared as described in Reference Example 2.

Reference Example 15

By using a method similar to that described in Reference Example 14, 5 γ -deoxy-5 γ -[N-(3-dimethylaminopropyl)acetamido]pristinamycin I_A (1.6 g) is obtained in the form of an ochre powder melting at 210° C.

An aqueous solution at a concentration of 10% of 5 γ -deoxy-5 γ -[N-(3-dimethylaminopropyl)acetamido]pristinamycin I_A (product M), in the form of hydrochloride, is obtained.

Reference Example 16

3-Dimethylaminopropanethiol (1.95 g) is added to a solution of 5 δ -methylenepristinamycin I_A (3.6 g) in a mixture of methanol (25 cc) and chloroform (5 cc), and then the solution obtained is stirred at a temperature of about 20° C. for 20 hours. The reaction mixture is then poured into distilled water (250 cc); the emulsion obtained is extracted 3 times with methylene chloride (250 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)]; fractions 10 to 38 are concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is triturated in ethyl ether (30 cc); the crystals obtained are separated off by filtration, and then dried under reduced pressure (27 Pa) at 20° C. In this manner, 5 δ -(3-dimethylaminopropyl)thiomethylpristinamycin I_A is obtained in the form of white crystals melting at 234° C.

NMR spectrum:

δ (ppm)	Form	Attribution
11.65	s (broad)	OH
8.70	d	6NH
8.40	d	1NH
7.80	dd	1'H ₆
7.45	m	1'H ₄ + 1'H ₅
7.27	m	
7.17	m	
7.05	d	
6.60	d	AB system
6.47	d	
		2 NH
5.87	ddd	1 β
5.83	d	6 α
5.24	m	5 α + 4 α
5.03	ddd	5 ϵ_1
4.85	dd	1 α
4.80	m	2 α
4.53	dd	3 α
3.53	m	3 δ_1
3.35	dd	
3.15	dd	ABX system
3.25	s	-CH ₂ -S-SCH ₂ -
		4 NCH ₃
3.25	m	3 δ_2
2.90	s	4N(CH ₃) ₂
2.90	m	4 β
2.50	dd	
2.40	t	
2.40 to 2.20	m	
2.25	s	-CH ₂ N(CH ₃) ₂
2	m	3 β_1
1.75	m	
1.8 to 1.45	m	-SCH ₂ CH ₂ CH ₂ -
1.30	d	2 β_1 + 2 β_2 + 3 γ_1
1.25 to 1.05	m	1 γ
0.9	t	3 γ_2 + 3 β_2
0.60	dd	2 γ
		5 β_2

An aqueous solution at a concentration of 10% of 5 δ -(3-dimethylaminopropyl)thiomethylpristinamycin I_A (product AA) is obtained with:

product AA	30 mg
0.1 N hydrochloric acid q.s.	0.3 cc

5 δ -methylenepristinamycin I_A can be prepared as follows:

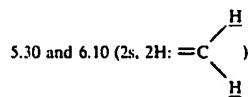
Sodium cyanoborohydride (0.43 g) is added to a solution of 5 δ -dimethylaminomethylenepristinamycin I_A (12 g) in tetrahydrofuran (230 cc) containing trifluoroacetic acid (1.2 cc). The solution obtained is stirred at a temperature of about 20° C. for 4 hours and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)]; fractions 4 to 15 are concentrated to dryness

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under reduced pressure (2.7 kpa) at 30° C. In this manner δ -methylenepristinamycin I_A (5.5 g) is obtained in the form of white crystals melting at 245° C.

NMR spectrum:

0.55 (d, 1H: $5\beta_2$)
2.40 (d, 1H: $5\beta_1$)
3.55 (dd, 1H: $5\epsilon_2$)
5.25 (m, 2H: $5\alpha + 5\epsilon_1$)



7.85 (dd, 1H: 1'H₆)

δ -Dimethylaminomethylenepristinamycin I_A can be prepared as follows:

tert-Butoxybis(dimethylamino)methane (230 cc) is added to a solution of pristinamycin I_A (46 g) in 1,2-dichloroethane (460 cc); the solution obtained is stirred at a temperature of about 20° C. for 18 hours. The reaction mixture is diluted with methylene chloride (1 liter) and then washed 3 times with a 0.4% strength aqueous solution of ammonium chloride (3 liters in total). The organic phase is dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is triturated with distilled water (600 cc); the mixture is filtered and the solid product is dried under reduced pressure (2.7 kPa) at 20° C. Crude δ -dimethylaminomethylenepristinamycin I_A (41 g) is obtained in the form of a beige powder. This product is of an adequate quality to be used as such as in the subsequent steps. It can, however, be purified as follows:

Crude δ -dimethylaminomethylenepristinamycin I_A (23.5 g) is purified by "flash" chromatography [eluent: chloroform-methanol (98-2 by volume)]. Fractions 16 to 25 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, δ -dimethylaminomethylenepristinamycin I_A (12 g) is obtained in the form of a beige powder melting at about 195° C.

NMR spectrum: 0.9 (t, 3H: 2 γ), 1.0 (dd, 1H: $5\beta_2$), 2.50 (d, 1H, $5\beta_1$), 3.10 (s, 6H: $-N(CH_3)_2$), 3.70 (d, 1H: $5\epsilon_2$), 5.50 (d, 1H: $5\epsilon_1$), 7.40 (s, 1H: $=CHN(CH_3)_2$), 7.75 (dd, 1H: 1'H₆).

Reference Example 17

By using a method similar to that described in Reference Example 16, but starting from δ -methylenevirginiamycin S (0.9 g) and 3-dimethylaminopropanethiol (0.52 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], and concentrating fractions 13 to 25 to dryness under reduced pressure (2.7 kPa) at 30° C., δ -(3-dimethylaminopropyl)thiomethylvirginiamycin S (0.3 g) is obtained in the form of a white powder melting at about 142° C.

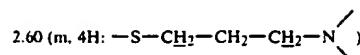
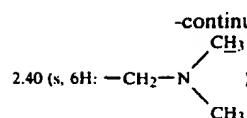
NMR spectrum:

0.45 (dd, 1H: $5\beta_2$)

1.90 (m, 2H: $-SCH_2CH_2CH_2N$)

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-continued



3.45 (d, 1H: $5\epsilon_2$)
4.85 (m, 3H including $5\epsilon_1$)
5.25 (dd, 1H: 5α)
7.78 (dd, 1H: 1'H₆)

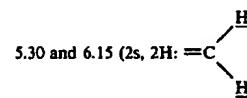
An aqueous solution at a concentration of 10% of δ -(3-dimethylaminopropyl)thiomethylvirginiamycin S (product AB), in the form of hydrochloride, is obtained with:

product AB	0.1 g
hydrochloric acid q.s.	1 cc

δ -Methylenevirginiamycin S can be prepared by a method similar to that described in Reference Example 16 for δ -methylenepristinamycin I_A, but starting from δ -dimethylaminomethylenevirginiamycin S (2 g) and sodium cyanoborohydride (74 mg). After purification by "flash" chromatography [eluent: chloroform-methanol (98-2 by volume)] and concentrating fractions 2 to 5 to dryness under reduced pressure (2.7 kPa) at 30° C., δ -methylenevirginiamycin S (1 g) is obtained in the form of a beige powder melting at about 190° C.

NMR spectrum:

0.35 (dd, 1H: $5\beta_2$)
2.45 (dd, 1H: $5\beta_1$)
3.55 (dd, 1H: $5\epsilon_2$)
5.25 (dd, 1H: $5\epsilon_1$)
5.25 (m, 1H: 5α)



7.75 (dd, 1I: 1'H₆)

δ -Dimethylaminomethylenevirginiamycin S can be obtained by using a method similar to that described in Reference Example 16 for δ -dimethylaminomethylenepristinamycin I_A, but starting from virginiamycin S (2 g) and bis(dimethylamino)tert-butoxymethane (10 cc) and, after purification by "flash" chromatography [eluent: chloroform-methanol (98-2 by volume)] and concentrating fractions 9 to 12 to dryness under reduced pressure (2.7 kPa) at 30° C., δ -dimethylaminomethylenevirginiamycin S (0.8 g) is obtained in the form of a yellow powder melting at about 175° C.

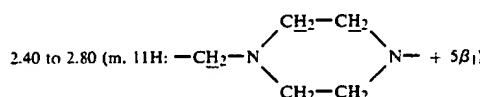
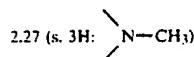
NMR spectrum: 0.9 (m, 4H: 2 γ + $5\beta_2$), 3.05 (s, 6H: $=CH-N(CH_3)_2$), 3.65 (d, 1H: $5\epsilon_2$), 4.85 (d, 1H: $5\epsilon_1$), 5.15 (dd, 1H: 5α), 7.10 to 7.40 (m: aromatics + $=CH-N<$), 7.70 (dd, 1H: 1'H₆). Reference Example 18

By using a method similar to that described in Reference Example 16, but starting from δ -methylenepristinamycin I_A (6 g) and 2-(4-methylpiperazinyl)ethane-

thiol (4 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (97-3 by volume)], and concentrating fractions 8 to 20 to dryness under reduced pressure (2.7 pKa) at 30° C., 5δ-[2-(4-methyl-piperazinyl)ethyl]thiomethylpristinamycin I_A (2.6 g) is obtained in the form of white crystals melting at 216° C.

NMR spectrum:

0.60 (dd, 1H: 5β₂)



5.05 (dd, 1H: 5ε₁)
5.27 (m, 2H: 5α + 4α)
7.85 (mt, 1H × 0.8: 1'H₆ 1st isomer)
7.95 (mt, 1H × 0.2: 1'H₆ 2nd isomer)

An aqueous solution at a concentration of 5% of 5δ-[2-(4-methyl-1-piperazinyl)ethyl]thiomethylpristinamycin I_A (product AC), in the form of hydrochloride, is obtained with:

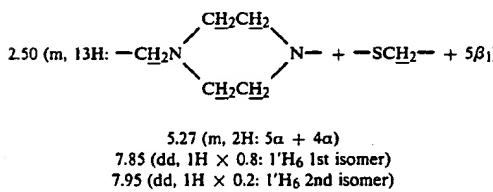
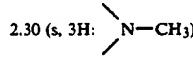
product AC	0.1 g
0.1 N hydrochloric acid	0.96 cc
distilled water q.s.	2 cc

Reference Example 19

By using a method similar to that described in reference Example 16, but starting from 5δ-methylenepristinamycin I_A (2 g) and 3-(4-methyl-1-piperazinyl)-propanethiol (3 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], and concentrating fractions 10 to 25 to dryness under reduced pressure (2.7 pKa) at 30° C., 5δ-[3-(4-methyl-1-piperazinyl)propyl]thiomethylpristinamycin I_A (1.9 g) is obtained in the form of a white powder melting at about 156° C.

NMR spectrum:

0.65 (dd, 1H: 5β₂)



An aqueous solution at a concentration of 10% of 5δ-[3-(4-methyl-1-piperazinyl)propyl]thiomethylpristinamycin I_A (product AD), in the form of hydrochloride, is obtained with:

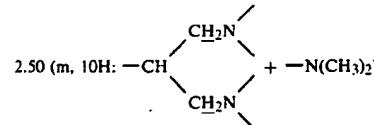
product AD	0.1 g
0.5 N hydrochloric acid	0.38 cc
distilled water q.s.	1 cc

Reference Example 20

By using a method similar to that described in Reference Example 16, but starting from 5δ-methylenepristinamycin I_A (4 g) and 1,3-bisdimethylamino-2-propanethiol (4 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 20 to 60 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-[1,3-bis(dimethylamino)-2-propyl]thiomethylpristinamycin I_A (0.59 g) is obtained in the form of a white powder melting at about 170° C.

NMR spectrum:

0.63 (dd, 1H: 5β₂)
2.40 (s, 6H: —N(CH₃)₂)



4.97 (s, 1H: 5ε₁)
5.30 (m, 2H: 5α + 4α)
7.85 (mt, 1H × 0.85: 1'H₆ 1st isomer)
7.95 (mt, 1H × 0.15: 1'H₆ 2nd isomer)

An aqueous solution at a concentration of 7.5% of 5δ-[1,3-bis(dimethylamino)-2-propyl]thiomethylpristinamycin I_A (product AE), in the form of hydrochloride, is obtained with:

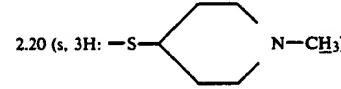
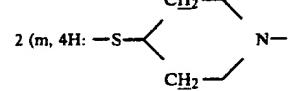
product AE	0.03 g
0.1 N hydrochloric acid	0.3 cc
distilled water q.s.	0.4 cc

Reference Example 21

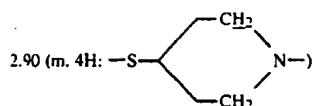
By using a method similar to that described in reference Example 16, but starting from 5δ-methylenepristinamycin I_A (3 g) and 2-methyl-4-mercaptopiperidine (0.97 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 10 to 16 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-(1-methyl-4-piperidyl)thiomethylpristinamycin I_A (1.1 g) is obtained in the form of a white powder melting at 260° C.

NMR spectrum:

0.6 (dd, 1H: 5β₂)



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-continued

2.35 (m, 1H: $\delta\beta_1$)5.30 (m, 2H: $\delta\alpha + \delta\alpha$)
7.85 (dd, 1H: 1H_6)

An aqueous solution at a concentration of 5% of 5 δ -(1-methyl-4-piperidyl)thiomethylpristinamycin I₄ (product AF), in the form of hydrochloride, is obtained with:

product AF	0.03 g
0.1 N hydrochloric acid	0.3 cc
distilled water q.s.	0.6 cc

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5

reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]; fractions 10 to 12 are concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner 5 δ -(2-dimethylaminoethyl)aminomethylenepristinamycin I₄ (3 g) is obtained in the form of a beige powder melting at about 180° C.

NMR spectrum:

0.90 (mt, 4H: $2\gamma + 2\beta_2$)
2.25 (mt, 6H: $-\text{N}(\text{CH}_3)_2$)2.50 (mt, 3H: $-\text{CH}_2\text{N}$ + $\delta\beta_1$)3.25 (mt, 2H: $\text{N}-\text{CH}_2-$)3.50 (mt, 2H: $5\epsilon_2 + 3\delta_1$)
4.90 (mt, 1H: $5\epsilon_1$)between 7.15 and 7.4 (m, 1H: $=\text{C}$ NH— H)9.90 (mt, 1H (exchangeable with D₂O): $-\text{NH}-$)

An aqueous solution at a concentration of 1% of 5 δ -(2-dimethylaminoethyl)aminomethylenepristinamycin I₄ (product AG) is obtained with:

product AG	0.1 g
distilled water q.s.	10 cc

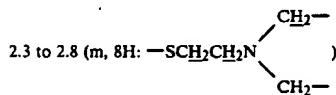
35

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Reference Example 22

By repeating Reference Example 16, but starting from 5 δ -methylenepristinamycin I₄ (2 g) and 2-diethylaminoethanethiol (0.66 g), after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 9 to 18 to dryness under reduced pressure (2.7 kPa) at 30° C., 5 δ -(2-diethylaminoethyl)thiomethylpristinamycin I₄ (0.8 g) is obtained in the form of a beige powder melting at 230° C.

NMR spectrum:

0.65 (dd, 1H: $\delta\beta_2$)
2.38 (d, 1H: $\delta\beta_1$)

3.15 (dd, 1H: $-\text{CH}_2\text{S}-$)
3.35 (dd, 1H: $-\text{CH}_2\text{S}-$)
5.01 (dd, 1H: $5\epsilon_1$)
7.81 (dd, 1H \times 0.9: 1H_6 1st isomer)
7.90 (dd, 1H \times 0.1: 1H_6 2nd isomer)

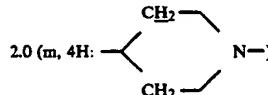
An aqueous solution at a concentration of 5% of 5 δ -(2-diethylaminoethyl)thiomethylpristinamycin I₄ (product AF₁) in the form of hydrochloride, is obtained with:

product AF ₁	30 mg
0.1 N hydrochloric acid	0.29 cc
distilled water q.s.	0.6 cc

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By using a method similar to that described in Reference Example 23, but starting from 5 δ -dimethylaminomethylenepristinamycin I₄ (13.8 g) and 4-amino-2-methylpiperidine (3.4 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (92.5-7.5 by volume)], and concentrating fractions 15 to 20 to dryness under reduced pressure (2.7 kPa) at 30° C., 5 δ -(1-methyl-4-piperidyl)aminomethylenepristinamycin I₄ (4.0 g) is obtained in the form of a yellow powder melting at 208° C.

NMR spectrum:

0.40 (m, 4H: $2\gamma + 2\beta_2$)2.35 (s, 3H: $\text{N}-\text{CH}_3$)2.45 (d, 1H: $\delta\beta_1$)

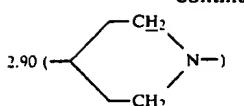
Reference Example 23

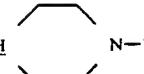
2-Dimethylaminoethylamine (5.3 g) is added dropwise, so as not to exceed 25° C., to a solution of 5 δ -dimethylaminomethylenepristinamycin I₄ (5.5 g) in acetic acid (60 cc). The solution obtained is stirred at a temperature of about 20° C. for 20 hours and is then poured slowly into a saturated aqueous solution of sodium bicarbonate; the mixture obtained is extracted twice with methylene chloride (750 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under

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-continued



3.20 (under unresolved bands. 1H: —CH— N—)

3.50 (d, 1H: 5ε₂)
4.85 (under unresolved bands. 1H: 5ε₁)
6.65 (d, 1H: =CHNH—)
9.70 (dd, 1H × 0.15: =CH—NH— 1st isomer)
10.03 (dd, 1H × 0.85: =CH—NH— 2nd isomer)

An aqueous solution at a concentration of 10% of
5δ-(1-methyl-4-piperidyl)aminomethylenepristinamycin

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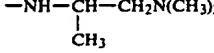
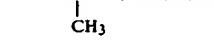
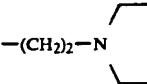
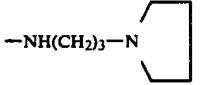
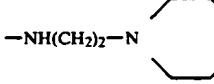
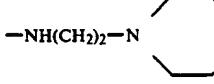
I_A (product AT), in the form of hydrochloride, is obtained with:

5	product AT 0.1 N hydrochloric acid distilled water q.s.	0.03 g 0.3 cc 0.3 cc
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4-Amino-2-methylpiperidine can be prepared by the method described by E. F. Elslager, L. M. Werbel, A. Curry, N. Headen, J. Johnson, J. Med. Chem. 17, 99 (1974).

By using the method of Reference Example 23, the following synergistins of general formula (V), which can be combined with the products according to the invention, are prepared.

[The symbols ——, X and Z are defined as at 2b) for the general formula (V) and, unless stated otherwise, Y denotes a dimethylamino radical].

Reference example	Y	R ₄	(1) Melting point (2) Solubility
25		—NH—(CH ₂) ₂ N(C ₂ H ₅) ₂	(1) Yellow powder M abt. 150° C. (2) 5% aqueous solution as hydrochloride
26		—NH(CH ₂) ₂ NHCH ₃	(1) Yellow powder M = 174° C. (2) 1% aqueous solution as hydrochloride
27		—NH(CH ₂) ₃ N(CH ₃) ₂	(1) Yellow powder M abt. 155° C. (2) 6.6% aqueous solution as hydrochloride
28		—NH—  —CH ₂ N(CH ₃) ₂	(1) Yellow powder M abt. 160° C. (2) 1% aqueous solution as hydrochloride
29		—NHCH ₂ CH—  —N(CH ₃) ₂	(1) Orange powder M abt. 175° C. (2) 10% aqueous solution as hydrochloride
30		—NH—  —(CH ₂) ₃ N(C ₂ H ₅) ₂	(1) Beige powder M abt. 160° C. (2) 1% aqueous solution as hydrochloride
31		—NH—(CH ₂) ₂ —  —N—	(1) Yellow powder M = 183° C. (2) 1% aqueous solution as hydrochloride
32		—NH(CH ₂) ₃ —  —N—	(1) Yellow powder M = 170° C. (2) 1% aqueous solution
33		—NH(CH ₂) ₂ —  —N—	(1) Yellow powder M = 162° C. (2) 1% aqueous solution as hydrochloride
34		—NH(CH ₂) ₂ —  —N—O—	(1) Beige powder M abt. 172° C. (2) 1% aqueous solution as hydrochloride

-continued

Reference example	Y	R ₄	(1) Melting point (2) Solubility
35			(1) Beige powder M abt. 160° C. (2) 1% aqueous solution as hydrochloride
36			(1) Beige powder M = 177° C. (2) 1% aqueous solution as hydrochloride
37	H		(1) Beige powder M abt. 195° C. (2) 5% aqueous solution as hydrochloride
38	-N(CH ₃) ₂		(1) Yellow powder M = 150° C. (2) 10% aqueous solution as hydrochloride
39	-N(CH ₃) ₂		(1) Yellow powder M = 138° C. (2) 10% aqueous solution as hydrochloride

Reference Example 40

2-Dimethylaminoethanethiol (2.1 g) is added to a 35 solution of 58-dimethylaminomethylenepristinamycin I_A (1.84 g) in acetic acid (40 cc). The solution obtained is stirred at a temperature of about 20° C. for 20 hours and is then poured slowly into a saturated aqueous solution of sodium bicarbonate; the mixture obtained is extracted 3 times with methylene chloride (400 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography 45 [eluent: chloroform-methanol (96:4 by volume)]; fractions 5 and 6 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, 58-(2-dimethylaminoethyl)thiomethylenepristinamycin I_A (0.8 g) is obtained in the form of a yellow 50 powder melting at about 150° C.

NMR spectrum: 0.68 (dd, 1H: 5β₁), 2.32 (s, 6H × 0.85: -CH₂N(CH₃)₂ 1st isomer), 2.35 (s, 6H × 0.15:

-CH₂N(CH₂ 2nd isomer), 2.45 (d, 1H: 5β₁), 2.65 (mt, 2H: -SCH₂-), 3.05 (t, 2H: -CH₂N<), 3.43 (dd, 1H: 5ε₂), 5.15 (in unresolved bands: 5ε₁), 7.60 (broad s, 1H: =CHS-), 7.83 (mt, 1H: 1'H₆, two isomers).

An aqueous solution at a concentration of 1% of 58-(2-dimethylaminoethyl)thiomethylenepristinamycin I_A (product AX), in the form of hydrochloride, is obtained with:

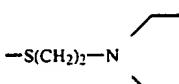
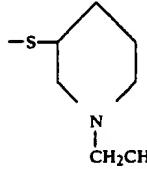
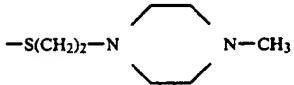
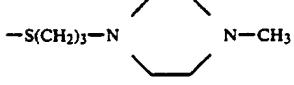
product AX	0.1 g
0.1 N hydrochloric acid	1 cc
distilled water q.s.	10 cc

By using the method of reference Example 40, the following synergists of general formula (V) which can be combined with the products according to the invention, are prepared.

[The symbols , X and Z are defined as in (2b) for the general formula (V), and, unless mentioned otherwise, Y denotes a dimethylamino radical].

Reference example	Y	R ₄	(1) Melting point (2) Solubility
41	-N(CH ₃) ₂	-S-(CH ₂) ₂ N(C ₂ H ₅) ₂	(1) Beige powder M abt. 192° C. (2) 1% aqueous solution as hydrochloride
42	-N(CH ₃) ₂	-S-(CH ₂) ₃ N(CH ₃) ₂	(1) Beige powder M abt. 170° C. (2) 1% aqueous solution as hydrochloride
43	-H	-S(CH ₂) ₃ N(CH ₃) ₂	(1) Beige powder M abt. 140° C. (2) 10% aqueous solution as hydrochloride

-continued

Reference example	Y	R ₄	(1) Melting point (2) Solubility
44	$-\text{N}(\text{CH}_3)_2$	$-\text{S}-\text{CH}_2-\underset{\substack{ \\ \text{CH}_3}}{\text{CH}}-\text{CH}_2\text{N}(\text{CH}_3)_2$	(1) Beige powder M = 234° C. (2) 10% aqueous solution as hydrochloride
45	$-\text{N}(\text{CH}_3)_2$	$-\text{S}-\text{CH}_2-\underset{\substack{\text{CH}_3 \\ \\ \text{CH}_3}}{\text{C}}-\text{N}(\text{CH}_3)_2$	(1) Beige powder M abt. 200° C. (2) 1% aqueous solution as hydrochloride
46	$-\text{N}(\text{CH}_3)_2$	$-\text{S}(\text{CH}_2)_2-\text{N}$ 	(1) Beige powder M abt. 180° C. (2) 1% aqueous solution as hydrochloride
47		$\begin{array}{c} \text{CH}_3 \\ \\ \text{N} \\ \\ -\text{S}-(\text{CH}_2)_2-\text{C} \\ \\ \text{CH}_3 \end{array}$	(1) Beige powder M abt. 215° C. (2) 0.6% aqueous solution as hydrochloride
48		$-\text{S}-\text{C}_6\text{H}_{11}-\text{N}-\text{CH}_3$	(1) Yellow powder M abt. 170° C. (2) 1% aqueous solution as hydrochloride
49		$-\text{S}-\text{C}_6\text{H}_{11}-\text{N}$  CH_2CH_3	(1) Beige powder M abt. 175° C. (2) 1% aqueous solution as hydrochloride
50		$-\text{S}-(\text{CH}_2)_2\text{N}-\text{C}_6\text{H}_{11}-\text{N}(\text{CH}_3)_2$	(1) Yellow powder M abt. 160° C. (2) 1% aqueous solution
51		$-\text{S}-\text{CH}[\text{CH}_2\text{N}(\text{CH}_3)_2]_2$	(1) Beige powder M abt. 190° C. (2) 1% aqueous solution as hydrochloride
52		$-\text{S}(\text{CH}_2)_2-\text{N}$  $\text{N}-\text{CH}_3$	(1) Beige powder M abt. 170° C. (2) 1% aqueous solution as hydrochloride
53		$-\text{S}(\text{CH}_2)_3-\text{N}$  $\text{N}-\text{CH}_3$	(1) Beige powder M abt. 190° C. (2) 10% aqueous solution as hydrochloride
54		$-\text{S}-\text{CH}_2-\underset{\substack{ \\ \text{CH}_3}}{\text{CH}}-\text{CH}_2-\text{N}(\text{CH}_3)_3^+$	(1) Ochre powder M abt. 150° C. (2) 1% aqueous solution as hydrochloride
55		$-\text{S}(\text{CH}_2)_2\text{SO}_3\text{H}$	(1) Yellow powder M > 280° C. (2) 5% aqueous solution

Reference Example 56

A solution of 5δ-(4-methylphenyl)sulphonyloxymethylenepristinamycin I_A (5.2 g) in methylene chloride (50 cc) is added to a solution of 1-(2-mercaptopropyl)-4-methylpiperazine (0.87 g) in ethanol (50 cc), to which sodium ethoxide (0.34 g) has been added. The reaction

65 mixture is stirred at a temperature of about 20° C. for 16 hours and is then diluted with methylene chloride (500 cc) and distilled water (100 cc). After stirring, the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concen-

trated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (97.5:2.5 by volume)]. Fractions 33 to 80 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, 5δ-[3-(4-methyl-1-piperazinyl)-2-propyl]thiomethylenepristinamycin I_A (1.25 g) is obtained in the form of a beige powder melting at about 195° C.

NMR spectrum:

0.70 (dd, 1H: 5β₂)

1.25 (d, 3H: —CH—CH₃)

2.30 (s, 3H: N—CH₃)

2.50 (m, 10H: —CH₂—N(CH₂CH₂)₂—N—CH₃)

3.40 (dd, 1H: 5ε₂)

7.85 (broad dd, 1H: 1'H₆)

An aqueous solution at a concentration of 10% of 5δ-[3-(4-methyl-1-piperazinyl)-2-propyl]thiomethylenepristinamycin I_A (product AAN) in the form of hydrochloride is obtained with:

product AAN	0.03 g
0.1 N hydrochloric acid	0.3 cc

1-(2-Mercaptopropyl)-4-methylpiperazine is prepared by heating a mixture of propylene sulphide (19 cc) and N-methylpiperazine (29 cc) at 100° C. for 16 hours. In this manner, a colourless oil (32 g) which distils at 105° C. at 1.3 kPa is obtained.

5δ-(4-Methylphenyl)sulphonyloxymethylenepristinamycin I_A can be obtained as follows:

Triethylamine (0.42 cc), and then p-toluenesulphonyl chloride (0.57 g) are added to a solution of 5δ-hydroxymethylenepristinamycin I_A (2.7 g) in methylene chloride (30 cc), at a temperature of about -30° C. The reaction mixture is then stirred at a temperature of about 20° C. for 2 hours and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C.; the residue obtained is purified by "flash" chromatography [eluent: methylene chloride-methanol (96:4 by volume)]. After concentrating fractions 4 to 6 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-(4-methylphenyl)sulphonyloxymethylenepristinamycin I_A (2.2 g) is obtained in the form of a white powder melting at about 265° C.

NMR spectrum:

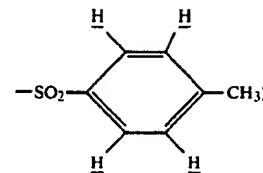
0.50 (dd, 1H: 5β₂)

2.35 (s, 3H: —SO₂—C₆H₄—CH₃)

3.30 (dd, 1H: 5ε₂)

-continued

5.25 (d, 1H: 5α)
5.30 (dd, 1H: 5ε₁)
7.35 to 7.90 (AB system + m, 8H: 4δ + 4ε +



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7.85 (dd, 1H: 1'H₆)

15 5δ-Hydroxymethylenepristinamycin I_A can be prepared as follows:

5δ-Dimethylaminomethylenepristinamycin I_A (10.6 g) is added to a 0.1N aqueous solution (420 cc) of hydrochloric acid. The solution obtained is then stirred at a temperature of about 20° C. for 3 hours. A saturated aqueous solution (30 cc) of sodium bicarbonate is then added dropwise so as to produce a pH of about 4. The product which precipitates is separated off by filtration and is then washed 3 times with distilled water (30 cc in total). After drying under reduced pressure (2.7 kPa) at a temperature of about 20° C., 5δ-hydroxymethylenepristinamycin I_A (9.5 g) is obtained in the form of a beige powder. This product is of adequate quality to be used as such in the subsequent steps. It can, however, be purified as follows:

Crude 5δ-hydroxymethylenepristinamycin I_A (9.5 g) is dissolved in ethyl acetate (50 cc); the solution obtained is poured onto silica gel (100 g) contained in a column 2.8 cm in diameter. Ethyl acetate (400 cc) is used for the initial elution, and the corresponding eluate is discarded; elution is then continued with ethyl acetate (1600 cc), and the corresponding eluate is concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner 5δ-hydroxymethylenepristinamycin I_A (6.3 g) is obtained in the form of white crystals melting at 220° C.

NMR spectrum: 0.69 (dd, 1H: 5β₂), 2.43 (d, 1H: 5β₁), 3.40 (d, 1H: 5ε₂), 4.0 to 4.2 (m, 3H: 4α + 5ε₁ + 5α), 8.15 (s, 1H: =CH—OH), 11.63 (broad s, 1H: =CH—OH).

Reference Example 57

By using a method similar to that described in Reference Example 56, 5δ-(3-dimethylamino-2-propyl)thiomethylenepristinamycin I_A (1 g) is obtained in the form of a yellow powder melting at 172° C.

An aqueous solution at a concentration of 5% of 5δ-(3-dimethylamino-2-propyl)thiomethylenepristinamycin I_A, in the form of hydrochloride, is obtained.

Reference Example 58

By using a method similar to that described in Reference Example 56, 5δ-(5-diethylamino-2-pentyl)thiomethylenepristinamycin I_A (1.32 g) is obtained in the form of a beige powder melting at about 185° C.

An aqueous solution at a concentration of 10% of 5δ-(5-diethylamino-2-pentyl)thiomethylenepristinamycin I_A in the form of hydrochloride, is obtained.

Reference Example 59

A solution of 5δ-[(4-methylphenyl)sulphonyloxymethylene]pristinamycin I_A (7.6 g) in tetrahydrofuran (60 cc) is cooled to a temperature of about -10° C. While

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maintaining this temperature, a solution is added to it, consisting of 2-dimethylaminoethanol (0.65 g) in tetrahydrofuran (60 cc), to which a 50% strength dispersion (0.35 g) of sodium hydride in mineral oil has been added. When the addition is complete, the temperature is allowed to rise slowly to about 20° C. The reaction mixture is stirred at this temperature for 24 hours and is then diluted with methylene chloride (500 cc) and washed with a saturated solution of ammonium chloride (2×50 cc). The organic phase is dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform:methanol (95:5 by volume)]. Fractions 12 to 17 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 25° C. In this manner, 58-(2-dimethylaminoethoxymethylene)pristinamycin I_A (1.5 g) is obtained in the form of a beige powder melting at about 160° C.

NMR spectrum:

0.65 (dd, 1H; $5\beta_2$), 2.3 (s, 6H; $-\text{N}(\text{CH}_3)_2$), 2.65 (m, 2H; $-\text{CH}_2\text{N}<$), 3.42 (dd, 1H; $5\epsilon_2$), 4.15 (t, 2H; $-\text{OCH}_2-$), 5.15 (d, 1H; $5\epsilon_1$), 7.45 (under the aromatics, 1H; $>\bar{\text{C}}=\text{CHO}$), 7.80 (dd, 1H; 1^{\prime}H_6).

An aqueous solution at a concentration of 1% of 5δ-(2-dimethylaminoethoxymethylene)pristinamycin I_A (product AAQ), in the form of hydrochloride, is obtained with:

product AAQ 0.03 g
 0.1 N hydrochloric acid 0.3 cc
 distilled water q.s. 3 cc

The present invention also relates to the medications consisting of a product of general formula (I) in free form or preferably in the form of a salt of addition with a pharmaceutically acceptable acid in the form of a combination with known synergistins or preferably with synergistins of general formula (V), the combination being moreover capable of containing any other pharmaceutically compatible, inert or physiologically active, product. The medications according to the invention can be administered by parenteral, oral, rectal or topical route.

Sterile compositions for parenteral administration can be, preferably, aqueous or nonaqueous solutions, suspensions or emulsions. Water, propylene glycol, a poly(ethylene glycol), vegetable oils, especially olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents, can be used as a solvent or vehicle. These compositions can also contain adjuvants, especially wetting agents, isotonizing agents, emulsifiers, dispersants and stabilizers. Sterilization can be carried out in various ways, for example by an asepticizing filtration, by adding sterilizing agents to the composition, by irradiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved in an injectable sterile medium at the time of use.

Tablets, pills, powders or granules can be employed as solid compositions for oral administration. In these compositions, the active product according to the invention (optionally combined with another pharmaceutically compatible product) is mixed with one or more inert diluents or adjuvants such as sucrose, lactose or starch. These compositions can also comprise sub-

stances other than diluents, for example a lubricant such as magnesium stearate.

Pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents such as water or parafin oil can be used as liquid compositions for oral administration. These compositions can also comprise substances other than the diluents, for example wetting agents, sweeteners or flavourings.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active substance, excipients such as cocoa butter, semi-synthetic glycerides or poly(ethylene glycols).

Compositions for topical administration can be, for example, creams, salves, lotions, eye lotions, mouth washes, nasal drops or aerosols.

In human therapy, the products according to the invention, which are combined with known synergistins or preferably with synergistins of general formula (V), are especially useful in the treatment of infections of a microbial origin. The dosages depend on the required effect and on the duration of treatment; for an adult, they are generally between 500 and 2000 mg per day by parenteral route, especially by an intravenous route such as a slow perfusion, the dosage of synergistin of general formula (V) itself being between 500 and 2000 mg per day.

As a general rule, the practitioner will determine the dosage which he or she considers the most suitable, depending on the age, weight and all the other individual characteristics of the subject to be treated.

The following example, given without implying any limitation, illustrates the compositions according to the invention.

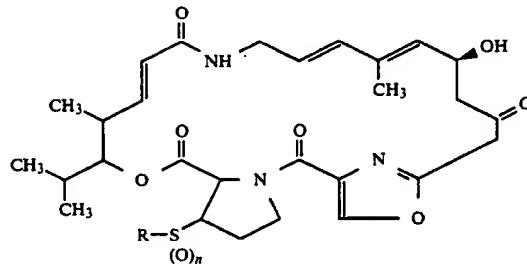
EXAMPLE

An injectable solution for perfusion, containing 1 g/l of active mixture having the following composition is prepared:

26-(2-diethylaminoethyl)sulphinyl-	0.6 g
pristinamycin II _B	
58-[2-(4-methyl-1-piperazinyl)ethyl]-	0.4 g
thiomethylpristinamycin I _A	
0.1 N aqueous solution of hydrochloric acid	12.7 cc
distilled water q.s.	1000 cc

We claim:

1. A pristinamycin II_B of the formula:



in which R denotes
ether a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidinyl
or 3- or 4-azepinyl radical each of which is unsubsti-
tuted or substituted by alkyl,
or alkyl of 2 to 4 carbon atoms substituted by 1 or 2
radicals chosen from phenyl, cycloalkylamino of 3 to

6 ring atoms, N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, alkylamino, dialkylamino, and dialkylcarbamoyloxy, the alkyl moieties of the said dialkylamino and dialkylcarbamoyloxy radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, and, if required, an oxygen, sulphur, or other nitrogen atom, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, 1-azepinyl, morpholino, thiomorpholino in the form of sulphoxide or sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-1-homopiperazinyl or imidazolyl radical, all of which may be unsubstituted or substituted by alkyl, or R denotes an alkyl of 2 to 4 carbon atoms substituted by 10 2- or 3-azetidinyl, 2- or 3-pyrrolidinyl, 2-, 3- or 4-piperidyl, 2-, 3- or 4-azepinyl, piperazinyl, 4-alkyl-piperazinyl, quinolyl, isoquinolyl, or imidazolyl radical, each of which is unsubstituted or substituted by 15 alkyl, these heterocyclic rings being linked to the alkyl of 2 to 4 carbon atoms by a carbon atom of the ring, n is 1 or 2 and, unless stated otherwise, the abovementioned alkyl radicals are linear or branched and contain 1 to 10 carbon atoms each, in its isomeric 20 forms or their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

2. A pristinamycin II_B according to claim 1, wherein R denotes alkyl of 2 to 4 carbon atoms substituted by 1 30 or 2 radicals chosen from phenyl, cycloalkylamino of 5 or 6 ring atoms, N-alkyl-N-cycloalkylamino of 5 or 6 ring atoms, alkylamino of 1 to 4 carbon atoms, or dialkylamino in which each alkyl is of 1 to 3 carbon atoms 35 or the alkyls form, with the nitrogen atom to which they are attached, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, or 1-azepinyl radical, or R denotes a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidyl or 3- or 4-azepinyl radical each of which is unsubstituted or substituted by 40 alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the said alkyl being in a 1- or a 2-position, in its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof. 45

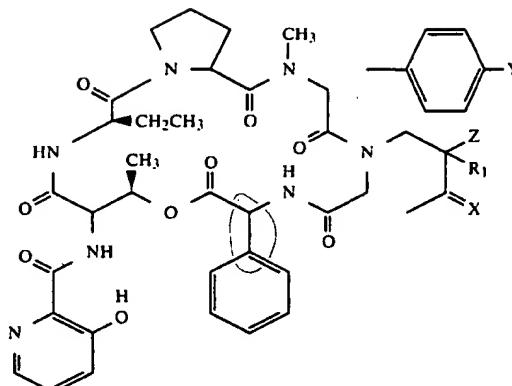
3. A pristinamycin II_B according to claim 1 which is 26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin II_B, its isomeric forms and their mixtures, or a pharmaceutically acceptable addition salt thereof. 50

4. A pristinamycin II_B according to claim 1 which is 26-[(2R)-2-dimethylaminobutyl]sulphonylpristinamycin II_B, its isomeric forms and their mixtures, or a pharmaceutically acceptable addition salt thereof. 55

5. A pristinamycin II_B according to claim 1 which is 26-(2-diethylaminopropyl)sulphonylpristinamycin II_B, its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

6. A pristinamycin II_B according to claim 1 which is 60 26-(2-diisopropylaminoethyl)sulphonylpristinamycin II_B, its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

7. An antibacterial or antimicrobial composition which 65 contains a pristinamycin II_B according to claim 1 in combination with a synergistically effective amount of a known synergistin or a soluble synergistin of formula:



in which Y denotes a hydrogen atom or a dimethylamino radical and

(1) either denotes a single bond, Z and R₁ denote a hydrogen atom and X denotes a radical of formula:



in which:

either R₂ denotes a hydrogen atom and R₃ denotes a hydroxy or alkyl radical unsubstituted or substituted by a carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl and azepinyl, or R₃ denotes a cycloalkyl radical containing 3 to 7 carbon atoms or a saturated 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these heterocyclic rings being unsubstituted or substituted by an alkyl radical on the nitrogen atom,

R₂ denotes a formyl or alkylcarbonyl radical and R₃ denotes an alkyl radical substituted by a carboxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl and azepinyl, or R₃ denotes a 4 to 7-membered heterocyclic ring chosen from azetidine, pyrrolidine, piperidine and azepine, these heterocyclic rings being unsubstituted or substituted by an alkyl radical on the nitrogen atom,

or R₂ and R₃, which are identical or different, each denote an alkyl radical which is unsubstituted or substituted by carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino whose alkyl radicals optionally form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl and azepinyl or R₂ and R₃ form, together with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine, morpholine and

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piperazine rings, optionally substituted by an alkyl radical.

(2) or denotes a double bond, X denotes an oxygen atom and Z denotes a radical of formula:



in which:

(a) either R₁ and R₅ each denote a hydrogen atom and R₄ denotes a 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical) or R₄ denotes an alkylthio radical substituted by one or two hydroxysulphonyl, alkylamino or dialkylamino (optionally substituted by a mercapto or dialkylamino radical) radicals or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercaptoalkyl radical), morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2, 3 or 4-piperidyl and 2- or 3-pyrrolidinyl (these last two rings being optionally substituted by an alkyl radical on the nitrogen atom),

(b) or R₁ and R₅ together form a valency bond and R₄ denotes a 3-pyrrolidinylamino, 3- or 4-piperidylamino, 3-pyrrolidinyloxy, 3- or 4-piperidyloxy, 3-pyrrolidinylthio, 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical on the nitrogen atom)

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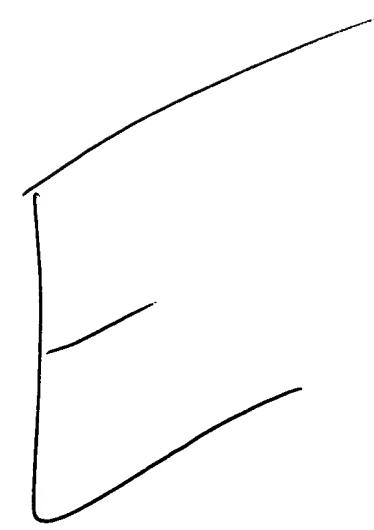
in the ring), or R₄ denotes an alkylamino, alkyloxy or alkylthio radical substituted by one or two hydroxy-sulphonyl, alkylamino, dialkylamino (optionally substituted by a dialkylamino radical), trialkylammonio or 4- or 5-imidazolyl radicals, or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercaptoalkyl radical), morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2, 3 or 4-piperidyl and 2- or 3-pyrrolidinyl (these two latter rings being optionally substituted by an alkyl radical on the nitrogen atom), it being understood that the alkyl radicals and alkyl moieties referred to in the symbols defined above contain 1 to 5 carbon atoms and form a linear or branched chain, if appropriate in the form of one of its isomers or their mixtures, and optionally in the form of an acid addition salt, a metal salt or an addition salt with a nitrogen-containing organic base.

8. A pharmaceutical composition according to claim 7 which also contains a compatible pharmaceutically acceptable carrier and/or adjuvant.

9. A pharmaceutical composition comprising an effective amount of a pristinamycin II_B according to claim 1 in association with a compatible pharmaceutically acceptable carrier and/or adjuvant.

10. Method of controlling bacterial growth which comprises exposing said bacteria to the effect of a pristinamycin II_B according to claim 1 in sufficient concentration to control said bacteria.

* * * * *



TLI | CEV

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In re U.S. Patent No. 4,668,669

Inventors: Jean-Claude Barriere et al.

Issued: May 26, 1987

Title: PRISTINAMYCIN II_B DERIVATIVES AND COMPOSITIONS
CONTAINING THEM

Enclosed:

1. Request for Certificate of Correction
2. PTO Form 1050 (10 pages - in duplicate)
3. Check in the amount of \$100.00

Date: 11/02/99

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Case Ref.: 3804.0055 CERTIFICATE OF CORRECTIONS BRANCH

CEVanHorn/C. Woods (M.D. 701) CRYSTAL PARK 3 - ROOM 918

ATTN: MINIKA BROWN



VS
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PATENT
Attorney Docket No. 3804.0055-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 4,668,669)
Inventors: Jean-Claude BARRIERE et al.)
Issue Date: May 26, 1987)
For: PRISTINAMYCIN II_B DERIVATIVES)
AND COMPOSITIONS CONTAINING)
THEM)

Certificate of Correction Branch

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

REQUEST FOR CERTIFICATE OF CORRECTION

Pursuant to 35 U.S.C. § 255 and 37 C.F.R. § 1.323, this is a request for the issuance of a Certificate of Correction in the above-identified patent. Two (2) copies of PTO Form 1050 are appended. The complete Certificate of Correction involves ten (10) pages.

The mistakes identified in the appended Form are of a clerical or typographical nature, or of minor character, and resulted from either an error of the Patent and Trademark Office or an error made in good faith by applicants. A certificate of correction is being filed to correct errors in various structured formulae and a typographical error or an error of minor character in the species recited in claim 5. No new matter is added because the compound as amended is explicitly supported in

Example 24 (col. 61) and no reexamination is required because the claimed compound is a species within allowed generic claim 1.

A check in the amount of \$100 (the fee set forth in 37 C.F.R. § 1.20(a)) is appended to cover the costs of issuing this Certificate. Should a check not be appended or should any additional fees be needed, authorization is hereby given to charge any fees due in connection with the filing of this request to Deposit Account No. 06-0916.

Issuance of the Certificate of Correction containing the correction is earnestly requested.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Dated: November 2, 1999

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

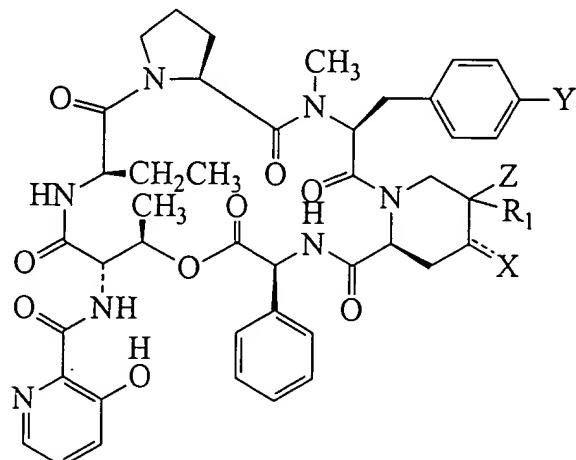
Page 1 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, second column, delete the second formula and substitute:



Mailing Address of Sender:

PATENT NO. 4,668,669

Finnegan, Henderson, Farabow
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

Page 2 of 10

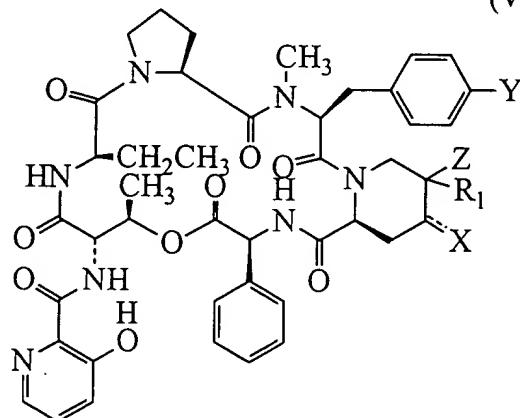
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, lines 1-18, delete Formula (V) and substitute:

(V)



Mailing Address of Sender:

PATENT NO. 4,668,669

Finnegan, Henderson, Farabow
Garrett & Dunner, L.L.P.
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FORM PTO 1050 (Rev.2-93)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

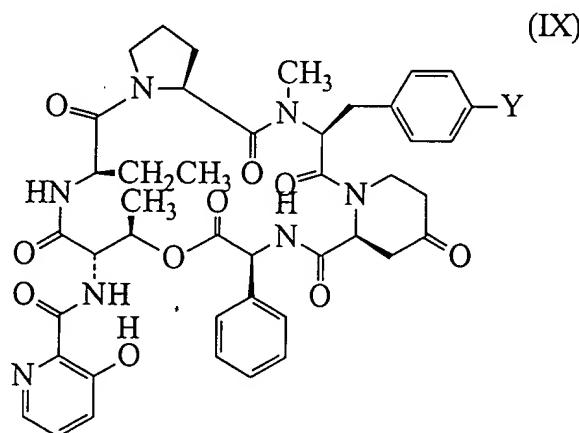
Page 3 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 15, lines 1-18, delete Formula (IX) and substitute:



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CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

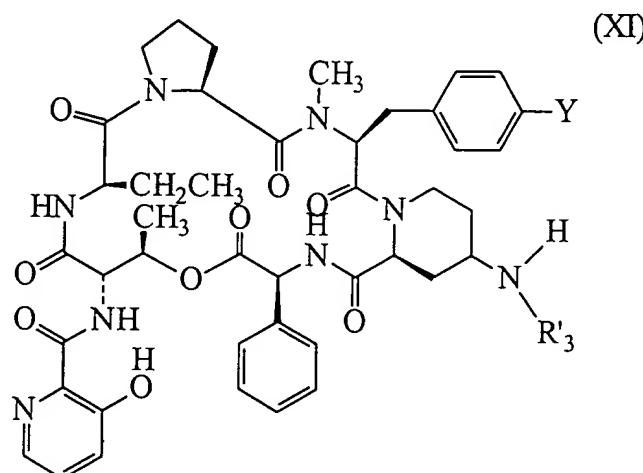
Page 4 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, lines 1-18, delete Formula (XI) and substitute:



Mailing Address of Sender:

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

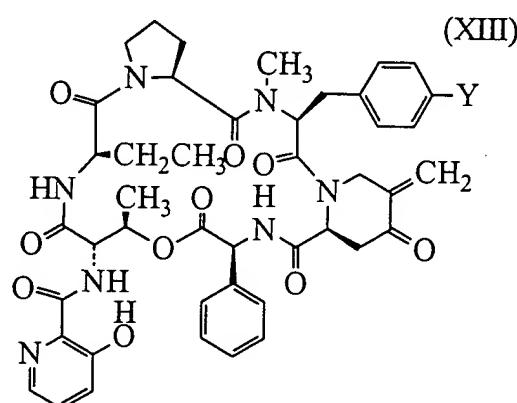
Page 5 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, lines 1-18, delete Formula (XIII) and substitute:



Mailing Address of Sender:

PATENT NO. 4,668,669

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Garrett & Dunner, L.L.P.
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

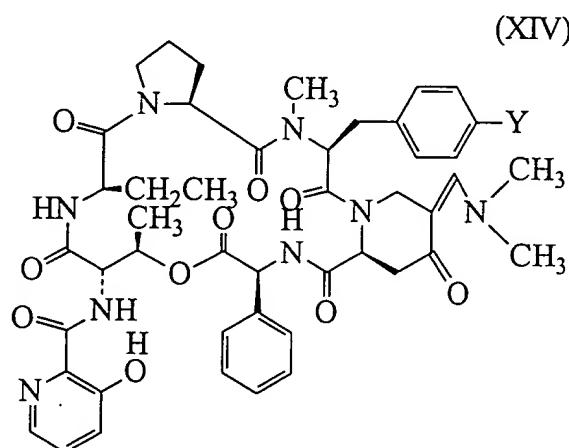
Page 6 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, lines 32-48, delete Formula (XIV) and substitute:



Mailing Address of Sender:

PATENT NO. 4,668,669

Finnegan, Henderson, Farabow
Garrett & Dunner, L.L.P.
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

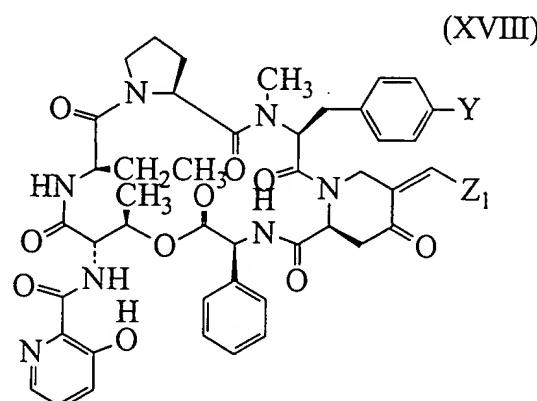
Page 7 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 18, lines 47-62, delete Formula (XVIII) and substitute:



Mailing Address of Sender:

PATENT NO. 4,668,669

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Garrett & Dunner, L.L.P.
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

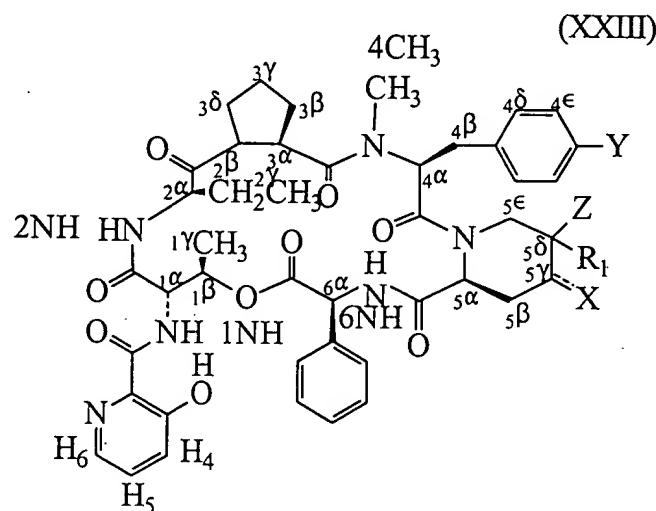
Page 8 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 23, lines 4-22, delete Formula (XXIII) and substitute:



Mailing Address of Sender:

PATENT NO. 4,668,669

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Garrett & Dunner, L.L.P.
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Washington, DC 20005-3315

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CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

Page 9 of 10

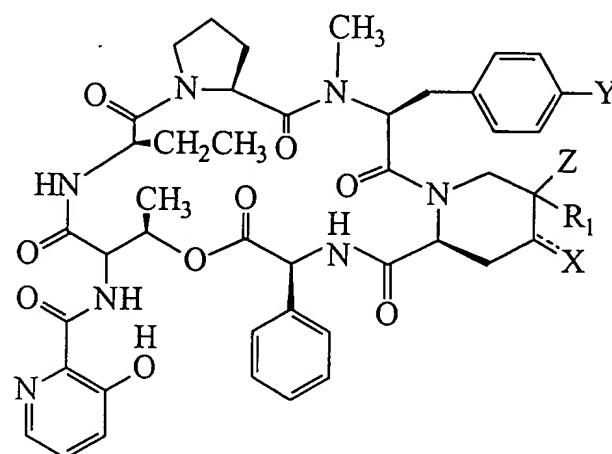
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 5, delete line 2 (col. 85, line 56) and substitute --26(2-diethylaminoethyl)sulphonylpristinamycin II_B--

In claim 7 (col. 86, lines 1-17) delete the formula and substitute:



Mailing Address of Sender:

PATENT NO. 4,668,669

Finnegan, Henderson, Farabow
Garrett & Dunner, L.L.P.
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Washington, DC 20005-3315

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

Page 10 of 10

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

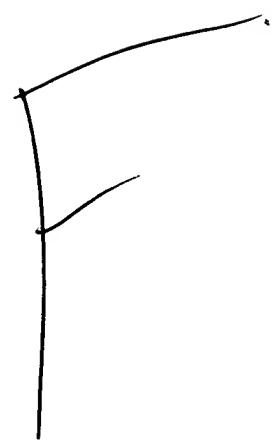
Claim 7, line 22 (col. 86), after "either" insert -- --

Mailing Address of Sender:

Finnegan, Henderson, Farabow
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315

PATENT NO. 4,668,669

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DEPOSIT ACCOUNTS

UNITED STATES DEPARTMENT OF COMMERCE

Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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M75W7

MARTIN F. SAVITZKY
RHONE-POULENC RORER INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE PA 19426-0107

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY SML YR ENT	STAT
1	4,668,669	185	3160	----	06/817,548	05/26/87	01/10/86	12 NO	PAID

ITM NBR	ATTY DKT NUMBER
1	EHM 24059

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231

G

RP59500 Synercid®

**IND 38,585 / NDA 50-748 and
IND 45,304/ NDA 50-747**

Chronology of major events - KEY MEETINGS

1994

04 May. 94	Subpart E program meeting
20 May 94	Microbiology teleconference
13 Jun 94	End Phase II Meeting

1995

17 April 95	Teleconference on Scientific content & format of NDA
-------------	--

1996

2 Apr 96	CMC Technical Meeting
30 Aug. 96	Biopharmaceutics teleconference
03 Sept. 96	Microbiology videoconference
05 Sept. 96	Clinical Issues teleconference
06 Nov. 96	Pre-NDA meeting

1997

15 Jan. 97	CANDA demonstration
30 May 97	Discussion on emergence of VRSA in Japan
14 Nov. 97	Discuss telephone Informed Consent in emergency situations.

1998

23 Jan 98	Teleconference to discuss clinical and microbiology issues
28 Jan 98	Videoconference to discuss/prepare for FDA Advisory Committee Mtg.
12 Feb 98	Meeting to discuss/prepare for FDA Advisory Committee Mtg.

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IND 38,585 / NDA 50-748 and
IND 45,304/ NDA 50-747

Chronology of major events - KEY MEETINGS

19 Feb. 98	FDA Advisory Committee meeting.
6 Mar 98	Teleconference: Questions about approvable letter for NDA 50-747 and draft VREF labeling
11 May 98	Phone Conference: Final agreement on vial and tray labeling
7 Aug 98	Phone Conference: IND on Clinical hold per GMP deficiencies at secondary manufacturing site
14 Aug 98	Phone conference: Synercid Emergency Use Program and supply allocation
1 Oct 98	Teleconference: Questions about approvable letter for NDA 50-748 and labeling

1999

3 Feb 99	Teleconference: Agree to submission specifics for alternate manufacturing site (Catalytica)
25 Feb 99	Teleconference: VREF Confirmatory Protocol #396 design discussion
28 Apr 99	Teleconference: VREF Confirmatory Protocol #396 design discussion
12 May 99	Final Label Review Meeting
24 May 99	Phone Conference: FDA Release of IND Clinical Hold
7 Jun 99	Teleconference: FDA agrees that labeling is final
22 Jul 99	Teleconference: FDA agrees to final pediatric development strategy

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**IND 38,585 / NDA 50-748 and
IND 45,304 / NDA 50-747**

KEY SUBMISSIONS / FDA REQUESTS

1991

31 Dec. 91	IND #38585 original submission
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1993

30 Mar. 93	Annual Report (30 Jan. 92 to 29 Jan. 93)
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1994

03 Mar. 94	Response to 02 Feb. 94 request for additional information
30 Mar. 94	Request for end of Phase II meeting
04 April 94	Annual Report (30 Jan. 93 to 29 Jan. 94)
24 May 94	IND 45,304 original submission
02 June 94	Providing preliminary phase III information
29 Aug. 94	Clarification of question requesting a response during the end of phase II meeting
22 Sep. 94	Providing desk copies of clinical info. requested on 26 Aug. 94
14 Nov. 94	Response to CMC questions/comments faxed to RPR on 25 Jul. 94.
30 Nov. 94	FDA fax containing 4 pages of chemistry comments.

1995

05 April 95	Annual Report (30 Jan. 94 to 29 Jan. 95)
16 May 95	Amendment/CMC : 15 chemistry comments
22 May 95	Authorization to export to Japan (request from RPR dated 13 mar. 95)
05 Sept. 95	Request for pre-NDA meeting.

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**IND 38,585 / NDA 50-748 and
IND 45,304 / NDA 50-747**

KEY SUBMISSIONS / FDA REQUESTS

30 Oct. 95	Change of manufacturing site for drug substance
------------	---

1996

13 March 96	Pre meeting CMC briefing document
29 March 96	Annual Report (30 Jan. 95 to 29 Jan. 96)
05 April 96	Briefing Documents for 17 April teleconference (after this submission teleconference was cancelled)
02 May 96	RPR requests authorization to export to France for use in Emergency compassionate clinical trials.
11 June 96	FDA requests a list of preclinical pharmacokinetic / toxicokinetic data that will be included in NDA.
02 July 96	Response to FDA request for information (CANDA + CRF's).
22 Oct. 96	Briefing document for pre-NDA meeting
14 Nov. 96	Phone contact to inform FDA of NDA delay

1997

02 April 97	Annual Report (30 Jan. 96 to 29 Jan. 97)
05 Sept. 97	NDA 50747 and 50748 submitted to FDA
08 Sept. 97	Sent to FDA : <ul style="list-style-type: none">• copy of the draft antimicrobial monograph,• CD containing the overall summary (item 2) of the NDA.• yield copy of the CMC section of NDA.
01 Oct. 97	Information regarding Investigator lists sent to FDA.
07 Oct. 97	Table formats to summarize reasons for non-evaluability sent to FDA.
05 Nov. 97	Response to FDA request for information about skin studies.

**IND 38,585 / NDA 50-748 and
IND 45,304 / NDA 50-747**

KEY SUBMISSIONS / FDA REQUESTS

04 Dec. 97	To FDA : 2 tables each providing list of patients with polymicrobial infections and list of reasons why CAP patients withdrew from study.
18 Dec. 97	Response to FDA request for information about microbiology.

1998

09 Jan. 98	<p>To FDA :</p> <ul style="list-style-type: none"> • copy of the report of the vial-container closure test results. • immersion test for the integrity of container closure system used for vials. • response to 31 Dec. 97 microbiology questions • response to 23 Dec. 97 microbiology questions
22 Jan. 98	Briefing document for FDA Advisory Committee Meeting.
2 Mar 98	CMC Submission RE: Lyophilizer, etc.
05 March 98	Approvable letter received for NDA 50-747.
09 March 98	Request for action preceding resolution of manufacturing issues
27 March 98	Provided list of ongoing studies, number of patients enrolled to date and approximate enrollment rate per month.
09 Apr 98	Provided listings for patients with total bilirubins and the liver safety board meeting minutes requested in 19 May fax
20 Apr 98	Annual Report (30 Jan 97 to 29 Jan 98)
06 Jul 98	Additional Microbiology analyses submitted
21 Jul 98	FDA request for Synercid Safety Data
7 Aug 98	FDA IND Clinical Hold Letter

RP59500 Synercid®

**IND 38,585 / NDA 50-748 and
IND 45,304 / NDA 50-747**

KEY SUBMISSIONS / FDA REQUESTS

7 Aug 98	FDA IND Clinical Hold Letter
10 Aug 98	IND Clinical Hold Response
14 Aug 98	Distribution of Synercid for Emergency Use during Clinical Hold
4 Sep 98	Approvable letter received for NDA 50-748
2 Oct 98	Updated Investigators Brochure
04 Nov 98	FDA Fax with questions RE: VREF Confirmatory Study #396
23 Nov 98	Updated Version of VREF Confirmatory Protocol #396
23 Nov 98	Final Study Report of Population PK Study
16 Dec 98	Response to Issues Raised in NDA 50-748 approvable letter plus Additional Safety data requested 21 Jul 98

1999

15 Jan 99	Response to Issues Raised in 50-747 approvable letter
02 Feb 99	RPR Fax documenting questions related to Catalytica Manufacturing site
04 Mar 99	Final Report Study #132
04 Mar 99	Final Report Study #152
24 Mar 99	Annual Report (30 Jan 98 to 29 Jan 99)
13 Apr 99	Final Labeling received from FDA by Fax
10 May 99	RPR fax with proposed labeling changes
24 May 99	Letter acknowledging lift of clinical hold
18 Jun 99	Promotional Materials for review - Wave 1

RP59500 Synercid®

**IND 38,585 / NDA 50-748 and
IND 45,304 / NDA 50-747**

KEY SUBMISSIONS / FDA REQUESTS

26 Aug 99	Promotional Materials for review - Wave 2
30 Aug 99	Written proposal regarding discontinuation of Emergency Use Program and use of Centeon-manufactured supplies
9 Sep 99	Promotional Materials for review - Wave 3
10 Sep 99	Promotional Materials for review - Wave 4
14 Sep 99	Promotional Materials for review - Wave 5
21 Sep 99	Approval letter for NDA 50-747 and 50-748
21 Sep 99	Fax copy of RPR press release

Rhône-Poulenc Rorer Central Research
Regulatory Affairs

APPLICATION CHRONOLOGY REPORT
Report Cover Page

Selection Criteria

App Number : 50747

Type : NDA

Drug Code: RP 59500

Trade Name: SYNERCID

Route of Administration : I.V.

Dosage Form : INFUSION

Generic Name: pristinamycin

500mg / vial.

Ending Date: 21-sep-1999

COMM DATE	COMM TYPE	DESCRIPTION
05-SEP-1997	ORIGINAL SUBMISSION	CMC DRUG SUBSTANCE
	ORIGINAL SUBMISSION	CMC DRUG PRODUCT
	ORIGINAL SUBMISSION	LABEL
	ORIGINAL SUBMISSION	4.3 CLINICAL SUMMARIES
	ORIGINAL SUBMISSION	CLINICAL CRF
	ORIGINAL SUBMISSION	PRECLINICAL PHARMACOLOGY
	ORIGINAL SUBMISSION	PRECLINICAL DRUG SAFETY
	ORIGINAL SUBMISSION	PRECLINICAL DRUG DISPO
	ORIGINAL SUBMISSION	PHARMACOKINETICS
	ORIGINAL SUBMISSION	MICROBIOLOGY
	ORIGINAL SUBMISSION	OTHER
15-SEP-1997	GENERAL CORRESP From FDA	CLINICAL STUDY
19-SEP-1997	GENERAL CORRESP To FDA	CLINICAL STUDY
27-OCT-1997	GENERAL CORRESP To FDA	CLINICAL STUDY
07-NOV-1997	GENERAL CORRESP To FDA	CLINICAL STUDY
12-NOV-1997	PHONE CALL	CMC DRUG SUBSTANCE
22-DEC-1997	PHONE CALL	MICROBIOLOGY STUDY
23-DEC-1997	PHONE CALL	CLINICAL STUDY
05-JAN-1998	AMENDMENT	SAFETY UPDATE
18-FEB-1998	GENERAL CORRESP To FDA	CMC DRUG PRODUCT
04-MAR-1998	GENERAL CORRESP To FDA	CLINICAL STUDY
05-MAR-1998	GENERAL CORRESP From FDA	CMC DRUG SUBSTANCE
	GENERAL CORRESP From FDA	CMC DRUG PRODUCT
	GENERAL CORRESP From FDA	LABEL
	GENERAL CORRESP From FDA	CLINICAL STUDY
	GENERAL CORRESP From FDA	OTHER APPROVABLE LETTER

COMM DATE	COMM TYPE	DESCRIPTION
05-MAR-1998	GENERAL CORRESP From FDA	OTHER FAX FROM FDA
05-MAR-1998	GENERAL CORRESP From FDA	OTHER COPY OF MINUTES FROM TELECONFERENCE
11-MAR-1998	GENERAL CORRESP To FDA	OTHER INTENTION TO AMEND APPLICATION
19-MAR-1998	GENERAL CORRESP From FDA	OTHER COPY OF MINUTES
03-APR-1998	GENERAL CORRESP To FDA	LABEL
14-APR-1998	GENERAL CORRESP To FDA	CLINICAL STUDY
14-APR-1998	GENERAL CORRESP To FDA	CLINICAL STUDY
15-APR-1998	GENERAL CORRESP From FDA	OTHER COPY OF MINUTES
24-APR-1998	GENERAL CORRESP To FDA	LABEL
05-MAY-1998	GENERAL CORRESP To FDA	CMC DRUG SUBSTANCE
05-MAY-1998	GENERAL CORRESP To FDA	LABEL
05-MAY-1998	GENERAL CORRESP To FDA	LABEL
05-MAY-1998	GENERAL CORRESP To FDA	LABEL
28-MAY-1998	GENERAL CORRESP From FDA	CLINICAL STUDY
02-JUN-1998	MEETING MINUTES	OTHER MEETING MINUTES
08-JUN-1998	GENERAL CORRESP To FDA	LABEL
08-JUN-1998	PHONE CALL	LABEL
09-JUN-1998	GENERAL CORRESP To FDA	CLINICAL STUDY
09-JUN-1998	PHONE CALL	CLINICAL STUDY
09-JUN-1998	PHONE CALL	CMC DRUG SUBSTANCE
30-JUN-1998	MEETING MINUTES	OTHER FDA TELECONFERENCE MEETING MINUTES
14-JUL-1998	GENERAL CORRESP To FDA	LABEL PACKAGE INSERT
14-JUL-1998	PHONE CALL	LABEL
14-JUL-1998	PHONE CALL	CMC DRUG SUBSTANCE
15-JUL-1998	PHONE CALL	CLINICAL STUDY
15-JUL-1998	PHONE CALL	CMC DRUG SUBSTANCE
16-JUL-1998	PHONE CALL	CLINICAL STUDY

COMM DATE	COMM TYPE	DESCRIPTION
21-JUL-1998	PHONE CALL	CLINICAL STUDY
21-JUL-1998	PHONE CALL	CLINICAL STUDY
23-JUL-1998	GENERAL CORRESP TO FDA	CLINICAL STUDY
23-JUL-1998	PHONE CALL	LABEL
24-JUL-1998	PHONE CALL	CLINICAL STUDY
27-JUL-1998	PHONE CALL	CLINICAL STUDY
28-JUL-1998	GENERAL CORRESP From FDA	CLINICAL STUDY
28-JUL-1998	PHONE CALL	CLINICAL STUDY
31-JUL-1998	GENERAL CORRESP To FDA	CMC DRUG SUBSTANCE
12-AUG-1998	GENERAL CORRESP To FDA	LABEL
12-AUG-1998	PHONE CALL	OTHER DISCUSSION
13-AUG-1998	PHONE CALL	OTHER
14-AUG-1998	PHONE CALL	CLINICAL STUDY
19-AUG-1998	PHONE CALL	CMC DRUG SUBSTANCE
26-AUG-1998	PHONE CALL	CLINICAL STUDY
26-AUG-1998	PHONE CALL	CMC DRUG SUBSTANCE
31-AUG-1998	PHONE CALL	CLINICAL STUDY
14-SEP-1998	PHONE CALL	CLINICAL STUDY
14-SEP-1998	PHONE CALL	OTHER ANTI-INFECTIVE ADVISORY MEETING
16-SEP-1998	GENERAL CORRESP To FDA	CLINICAL CRF
16-SEP-1998	PHONE CALL	OTHER ANTI-INFECTIVE ADVISORY MEETING
21-SEP-1998	PHONE CALL	OTHER ANTI-INFECTIVE ADVISORY MEETING
24-SEP-1998	PHONE CALL	LABEL PACKAGE INSERT
08-OCT-1998	PHONE CALL	CLINICAL STUDY
19-OCT-1998	GENERAL CORRESP To FDA	LABEL
20-OCT-1998	PHONE CALL	OTHER MEETING MINUTES

COMM DATE	COMM TYPE	DESCRIPTION
22-OCT-1998	GENERAL CORRESP TO FDA	OTHER REQUEST FOR COMMENTS
27-OCT-1998	PHONE CALL	CLINICAL STUDY
29-OCT-1998	PHONE CALL	OTHER CONFIRM AGREEMENT
04-NOV-1998	GENERAL CORRESP From FDA	CLINICAL STUDY
23-NOV-1998	GENERAL CORRESP	CLINICAL STUDY
02-DEC-1998	GENERAL CORRESP	CLINICAL STUDY
02-DEC-1998	PHONE CALL	CLINICAL STUDY
08-DEC-1998	PHONE CALL	CLINICAL STUDY
10-DEC-1998	PHONE CALL	OTHER PROPOSAL
11-DEC-1998	GENERAL CORRESP To FDA	CLINICAL STUDY
14-DEC-1998	PHONE CALL	CMC DRUG PRODUCT
17-DEC-1998	PHONE CALL	CLINICAL STUDY
17-DEC-1998	GENERAL CORRESP To FDA	LABEL
18-DEC-1998	GENERAL CORRESP To FDA	CMC DRUG SUBSTANCE
29-DEC-1998	PHONE CALL	CMC DRUG PRODUCT
05-JAN-1999	PHONE CALL	CLINICAL SAFETY REPORT
05-JAN-1999	PHONE CALL	CLINICAL SAFETY REPORT
13-JAN-1999	PHONE CALL	CLINICAL STUDY
15-JAN-1999	GENERAL CORRESP To FDA	CLINICAL STUDY
19-JAN-1999	PHONE CALL	OTHER DISCUSS MISC ISSUES
21-JAN-1999	PHONE CALL	OTHER DISCUSS MISC ISSUES
25-JAN-1999	GENERAL CORRESP To FDA	CLINICAL STUDY
25-JAN-1999	PHONE CALL	LABEL LABEL REVIEW MEETING
	PHONE CALL	OTHER

COMM DATE	COMM TYPE	DESCRIPTION
26-JAN-1999	GENERAL CORRESP TO FDA	OTHER
26-JAN-1999	PHONE CALL	OTHER
29-JAN-1999	GENERAL CORRESP TO FDA	CLINICAL
01-FEB-1999	PHONE CALL	OTHER
02-FEB-1999	GENERAL CORRESP TO FDA	CMC
02-FEB-1999	PHONE CALL	CMC
09-FEB-1999	PHONE CALL	LABEL
18-FEB-1999	PHONE CALL	LABEL
22-FEB-1999	MEETING MINUTES	CLINICAL
	MEETING MINUTES	CMC
23-FEB-1999	GENERAL CORRESP TO FDA	OTHER
23-FEB-1999	PHONE CALL	CLINICAL
	PHONE CALL	LABEL
	PHONE CALL	OTHER
25-FEB-1999	PHONE CALL	CLINICAL
01-MAR-1999	GENERAL CORRESP TO FDA	OTHER
04-MAR-1999	GENERAL CORRESP TO FDA	CLINICAL
09-MAR-1999	PHONE CALL	CMC
10-MAR-1999	MEETING MINUTES	CLINICAL
15-MAR-1999	GENERAL CORRESP TO FDA	CLINICAL
17-MAR-1999	PHONE CALL	LABEL
23-MAR-1999	GENERAL CORRESP TO FDA	CLINICAL
23-MAR-1999	PHONE CALL	LABEL
26-MAR-1999	GENERAL CORRESP TO FDA	CMC
29-MAR-1999	PHONE CALL	LABEL
07-APR-1999	PHONE CALL	LABEL

COMM DATE	COMM TYPE	DESCRIPTION
08-APR-1999	MEETING MINUTES	CLINICAL STUDY
13-APR-1999	GENERAL CORRESP FROM FDA	LABEL
13-APR-1999	PHONE CALL	LABEL
13-APR-1999	PHONE CALL	LABEL
27-APR-1999	GENERAL CORRESP TO FDA	LABEL
27-APR-1999	GENERAL CORRESP TO FDA	LABEL
28-APR-1999	PHONE CALL	CLINICAL STUDY
03-MAY-1999	PHONE CALL	LABEL
10-MAY-1999	GENERAL CORRESP TO FDA	LABEL
10-MAY-1999	PHONE CALL	LABEL
12-MAY-1999	GENERAL CORRESP TO FDA	OTHER
13-MAY-1999	PHONE CALL	CLINICAL STUDY
18-MAY-1999	GENERAL CORRESP From FDA	LABEL
20-MAY-1999	GENERAL CORRESP TO FDA	LABEL
20-MAY-1999	PHONE CALL	OTHER
25-MAY-1999	GENERAL CORRESP TO FDA	CMC
25-MAY-1999	GENERAL CORRESP TO FDA	CMC
26-MAY-1999	GENERAL CORRESP TO FDA	CLINICAL
26-MAY-1999	GENERAL CORRESP TO FDA	CLINICAL
26-MAY-1999	PHONE CALL	OTHER
02-JUN-1999	PHONE CALL	LABEL
04-JUN-1999	AMENDMENT	CMC
04-JUN-1999	GENERAL CORRESP TO FDA	CMC
07-JUN-1999	MEETING MINUTES	CLINICAL
07-JUN-1999	PHONE CALL	OTHER
10-JUN-1999	PHONE CALL	OTHER

COMM DATE	COMM TYPE	DESCRIPTION
17-JUN-1999	PHONE CALL	CLINICAL STUDY
18-JUN-1999	GENERAL CORRESP TO FDA	LABEL
21-JUN-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
24-JUN-1999	MEETING MINUTES	CLINICAL STUDY
24-JUN-1999	PHONE CALL	OTHER NUMEROUS ISSUES
01-JUL-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
01-JUL-1999	PHONE CALL	OTHER NUMEROUS ISSUES
06-JUL-1999	MEETING MINUTES	LABEL
07-JUL-1999	PHONE CALL	OTHER NUMEROUS ISSUES
08-JUL-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
08-JUL-1999	GENERAL CORRESP TO FDA	CLINICAL PROTOCOL AMENDMENT
08-JUL-1999	PHONE CALL	LABEL PACKAGE INSERT
15-JUL-1999	PHONE CALL	OTHER NUMEROUS ISSUES
21-JUL-1999	GENERAL CORRESP From FDA	LABEL COPY OF RESPONSE
21-JUL-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
21-JUL-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
21-JUL-1999	GENERAL CORRESP From FDA	LABEL
22-JUL-1999	PHONE CALL	CMC DRUG PRODUCT
22-JUL-1999	PHONE CALL	OTHER REQUEST
23-JUL-1999	AMENDMENT	CMC DRUG PRODUCT
26-JUL-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
26-JUL-1999	GENERAL CORRESP TO FDA	CMC DRUG PRODUCT
26-JUL-1999	PHONE CALL	CMC DRUG PRODUCT
28-JUL-1999	AMENDMENT	CMC DRUG PRODUCT
02-AUG-1999	GENERAL CORRESP To FDA	OTHER LETTER
04-AUG-1999	GENERAL CORRESP To FDA	OTHER FAX COPY

COMM DATE	COMM TYPE	DESCRIPTION
04-AUG-1999	GENERAL CORRESP TO FDA	CMC
04-AUG-1999	PHONE CALL	OTHER
06-AUG-1999	GENERAL CORRESP TO FDA	CLINICAL
06-AUG-1999	GENERAL CORRESP TO FDA	STUDY
09-AUG-1999	GENERAL CORRESP From FDA	LABEL
09-AUG-1999	GENERAL CORRESP From FDA	CLINICAL
09-AUG-1999	PHONE CALL	STUDY
10-AUG-1999	GENERAL CORRESP TO FDA	OTHER
10-AUG-1999	GENERAL CORRESP TO FDA	NUMEROUS ISSUES
10-AUG-1999	GENERAL CORRESP From FDA	LABEL
10-AUG-1999	GENERAL CORRESP From FDA	PACKAGE INSERT
16-AUG-1999	PHONE CALL	DRUG PRODUCT
17-AUG-1999	GENERAL CORRESP TO FDA	OTHER
17-AUG-1999	GENERAL CORRESP TO FDA	REQUEST FOR TELECON
17-AUG-1999	GENERAL CORRESP TO FDA	LABEL
17-AUG-1999	GENERAL CORRESP TO FDA	PACKAGE INSERT
17-AUG-1999	GENERAL CORRESP TO FDA	STUDY
17-AUG-1999	GENERAL CORRESP TO FDA	CLINICAL
17-AUG-1999	GENERAL CORRESP TO FDA	DISCUSSION
17-AUG-1999	PHONE CALL	REQUEST
18-AUG-1999	GENERAL CORRESP TO FDA	DRUG PRODUCT
19-AUG-1999	PHONE CALL	DISCUSSION
26-AUG-1999	GENERAL CORRESP TO FDA	OTHER
26-AUG-1999	GENERAL CORRESP TO FDA	LABEL
30-AUG-1999	GENERAL CORRESP TO FDA	CMC
30-AUG-1999	GENERAL CORRESP TO FDA	DRUG PRODUCT
31-AUG-1999	PHONE CALL	CLINICAL
02-SEP-1999	GENERAL CORRESP TO FDA	CMC
02-SEP-1999	GENERAL CORRESP TO FDA	STUDY
02-SEP-1999	GENERAL CORRESP From FDA	CLINICAL
02-SEP-1999	GENERAL CORRESP From FDA	DISCUSSION
02-SEP-1999	GENERAL CORRESP From FDA	LABEL
02-SEP-1999	PHONE CALL	DRUG PRODUCT

COMM DATE	COMM TYPE	DESCRIPTION
08-SEP-1999	GENERAL CORRESP TO FDA	LABEL
08-SEP-1999	PHONE CALL	OTHER INFORMATION
09-SEP-1999	GENERAL CORRESP TO FDA	LABEL
10-SEP-1999	GENERAL CORRESP TO FDA	LABEL
10-SEP-1999	GENERAL CORRESP TO FDA	LABEL
10-SEP-1999	GENERAL CORRESP TO FDA	LABEL
14-SEP-1999	GENERAL CORRESP TO FDA	DRAFT PRESS RELEASE
14-SEP-1999	GENERAL CORRESP TO FDA	OTHER
14-SEP-1999	GENERAL CORRESP TO FDA	LABEL
14-SEP-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
14-SEP-1999	GENERAL CORRESP TO FDA	LABEL
14-SEP-1999	PHONE CALL	OTHER DISCUSSION
15-SEP-1999	PHONE CALL	LABEL
16-SEP-1999	PHONE CALL	OTHER DISCUSSION
20-SEP-1999	PHONE CALL	OTHER NOTIFY REPORT
21-SEP-1999	GENERAL CORRESP From FDA	OTHER APPROVAL LETTER FOR NDA 50-747 AND NDA 50-748
21-SEP-1999	GENERAL CORRESP From FDA	LABEL FDA COMMENTS ON DRAFT PRESS RELEASE
21-SEP-1999	GENERAL CORRESP From FDA	LABEL RESPONSE
21-SEP-1999	GENERAL CORRESP From FDA	LABEL OTHER RECOMMENDATIONS
21-SEP-1999	GENERAL CORRESP To FDA	LABEL FAX COPY OF PRESS RELEASE
21-SEP-1999	GENERAL CORRESP From FDA	OTHER FDA FAX COPY OF 21-SEP-99 APPROVAL ACTION LETTER
21-SEP-1999	PHONE CALL	LABEL DISCUSSION
21-SEP-1999	PHONE CALL	OTHER DISCUSSION

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Regulatory Affairs

APPLICATION CHRONOLOGY REPORT
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Selection Criteria

App Number : 45304

Type : IND

Drug Code : RP 59500

Trade Name: SYNERCID

Route of Administration : INJECTION

Dosage Form : INFUSION

Generic Name : pristinamycin

RP57669/54476 500mg.

Ending Date: 21-sep-1999

COMM DATE	COMM TYPE	DESCRIPTION
24-MAY-1994	ORIGINAL SUBMISSION	OTHER INVESTIGATOR'S BROCHURE
	ORIGINAL SUBMISSION	CLINICAL STUDY
26-MAY-1994	GENERAL CORRESP From FDA	OTHER FDA ACKNOWLEDGEMENT OF RECEIPT OF ORIG IND ON 24-MAY-94
06-JUN-1994	AMENDMENT	CLINICAL CRF
07-JUN-1994	AMENDMENT	OTHER EXTRA COPIES
07-JUN-1994	AMENDMENT	CLINICAL STUDY
07-JUN-1994	AMENDMENT	OTHER REQUEST FOR TELEPHONE CONFERENCE
11-JUL-1994	PHONE CALL	CMC DRUG PRODUCT
12-JUL-1994	AMENDMENT	CLINICAL STUDY
14-JUL-1994	GENERAL CORRESP To FDA	CMC DRUG PRODUCT
25-JUL-1994	AMENDMENT	CLINICAL STUDY
25-JUL-1994	GENERAL CORRESP From FDA	CMC DRUG SUBSTANCE
25-JUL-1994	PHONE CALL	CLINICAL STUDY
26-JUL-1994	PHONE CALL	CLINICAL STUDY
27-JUL-1994	AMENDMENT	CLINICAL STUDY
27-JUL-1994	PHONE CALL	OTHER CLARIFICATION OF SEVERAL POINTS
29-JUL-1994	GENERAL CORRESP To FDA	CLINICAL CRF
08-AUG-1994	PHONE CALL	CLINICAL STUDY
16-AUG-1994	PHONE CALL	CLINICAL STUDY
09-SEP-1994	AMENDMENT	CLINICAL SUMMARY
19-SEP-1994	PHONE CALL	OTHER SCHEDULE PRE-NDA MEETING
26-SEP-1994	PHONE CALL	CMC DRUG PRODUCT
11-OCT-1994	AMENDMENT	CLINICAL STUDY
	AMENDMENT	CLINICAL PROTOCOL AMENDMENT
28-OCT-1994	PHONE CALL	MICROBIOLOGY VARIOUS ISSUES
31-OCT-1994	AMENDMENT	CLINICAL STUDY

COMM DATE	COMM TYPE	DESCRIPTION
04-NOV-1994	AMENDMENT	CLINICAL STUDY
04-NOV-1994	AMENDMENT	CLINICAL STUDY
07-NOV-1994	AMENDMENT	CLINICAL STUDY
07-NOV-1994	PHONE CALL	MICROBIOLOGY
07-NOV-1994	PHONE CALL	OTHER VARIOUS ISSUES
08-NOV-1994	AMENDMENT	CLINICAL STUDY
10-NOV-1994	AMENDMENT	CLINICAL STUDY
10-NOV-1994	PHONE CALL	PHARMACOKINETICS
14-NOV-1994	AMENDMENT	CLINICAL STUDY
14-NOV-1994	AMENDMENT	CLINICAL STUDY
14-NOV-1994	AMENDMENT	CMC DRUG
14-NOV-1994	AMENDMENT	CMC DRUG
15-NOV-1994	AMENDMENT	CLINICAL STUDY
23-NOV-1994	PHONE CALL	OTHER DISCUSS VARIOUS ISSUES
06-DEC-1994	AMENDMENT	CLINICAL OTHER MEETING REQUEST
15-DEC-1994	AMENDMENT	CMC DRUG PRODUCT
20-DEC-1994	AMENDMENT	OTHER ENCLOSED A LIST OF ISSUES
23-DEC-1994	FDA REPORT	CLINICAL SAFETY REPORT
03-JAN-1995	AMENDMENT	CLINICAL STUDY
05-JAN-1995	FDA REPORT	CLINICAL SAFETY REPORT
05-JAN-1995	PHONE CALL	OTHER PRE-NDA MEETING DISCUSSED
	PHONE CALL	PRECLINICAL STUDY
	PHONE CALL	CLINICAL STUDY
12-JAN-1995	MEETING MINUTES	OTHER PRESENTED MEETING MINUTES
12-JAN-1995	MEETING MINUTES	OTHER PROVIDED MEETING MINUTES

COMM DATE	COMM TYPE	DESCRIPTION
12-JAN-1995	PHONE CALL	OTHER FOLLOW-UP
12-JAN-1995	PHONE CALL	OTHER PRE-NDA MEETING
18-JAN-1995	PHONE CALL	OTHER DISCUSS SCHEDULING THE PRE-NDA MEETING
30-JAN-1995	AMENDMENT	CMC DRUG PRODUCT
31-JAN-1995	PHONE CALL	OTHER RECEIVE FEEDBACK RE: FDA'S INTERNAL MEETING
03-FEB-1995	PHONE CALL	OTHER DISCUSS PROPOSAL
07-FEB-1995	AMENDMENT	CLINICAL STUDY
08-FEB-1995	GENERAL CORRESP TO FDA	CLINICAL STUDY
	GENERAL CORRESP TO FDA	CLINICAL CRF
08-FEB-1995	GENERAL CORRESP From FDA	CMC DRUG SUBSTANCE
15-FEB-1995	AMENDMENT	CLINICAL PROTOCOL AMENDMENT
21-FEB-1995	PHONE CALL	OTHER POSTPONE PRE-NDA MEETING
06-MAR-1995	AMENDMENT	CLINICAL STUDY
07-MAR-1995	PHONE CALL	OTHER PROTOCOL
10-MAR-1995	AMENDMENT	CLINICAL STUDY
10-MAR-1995	GENERAL CORRESP To FDA	CLINICAL STUDY
13-MAR-1995	PHONE CALL	OTHER APRIL 3 MEETING
16-MAR-1995	PHONE CALL	OTHER APRIL 10TH MEETING
16-MAR-1995	PHONE CALL	CLINICAL SAFETY
17-MAR-1995	FDA REPORT	CLINICAL SAFETY
17-MAR-1995	GENERAL CORRESP From FDA	OTHER FDA FAX TO CONFIRM MEETING
22-MAR-1995	PHONE CALL	OTHER
24-MAR-1995	FDA REPORT	5 CLINICAL SAFETY REPORTS
03-APR-1995	AMENDMENT	OTHER PROVIDED PRE-MEETING BRIEFING PACKAGE
05-APR-1995	FDA REPORT	ANNUAL RPT

COMM DATE	COMM TYPE	DESCRIPTION
05-APR-1995	PHONE CALL	OTHER
05-APR-1995	PHONE CALL	OTHER
06-APR-1995	AMENDMENT	CLINICAL
05-MAY-1995	MEETING MINUTES	LABEL
11-MAY-1995	AMENDMENT	CLINICAL
12-MAY-1995	AMENDMENT	CLINICAL
16-MAY-1995	AMENDMENT	CLINICAL
02-JUN-1995	PHONE CALL	CLINICAL
06-JUN-1995	FDA REPORT	CLINICAL
27-JUN-1995	AMENDMENT	CLINICAL
10-JUL-1995	AMENDMENT	CLINICAL
17-AUG-1995	PHONE CALL	CLINICAL
18-AUG-1995	PHONE CALL	OTHER
22-AUG-1995	AMENDMENT	CLINICAL
23-AUG-1995	FDA REPORT	CLINICAL
05-SEP-1995	AMENDMENT	CMC
12-SEP-1995	PHONE CALL	CLINICAL
21-SEP-1995	AMENDMENT	CLINICAL
21-SEP-1995	FDA REPORT	CLINICAL
28-SEP-1995	GENERAL CORRESP To FDA	CLINICAL
03-OCT-1995	FDA REPORT	CLINICAL
04-OCT-1995	FDA REPORT	CLINICAL
04-OCT-1995	FDA REPORT	CLINICAL
06-OCT-1995	AMENDMENT	OTHER
24-OCT-1995	AMENDMENT	CLINICAL

COMM DATE	COMM TYPE	DESCRIPTION
30-OCT-1995	AMENDMENT	CMC
30-OCT-1995	AMENDMENT	CLINICAL
09-NOV-1995	FDA REPORT	CLINICAL
10-NOV-1995	AMENDMENT	CLINICAL
17-NOV-1995	PHONE CALL	OTHER
06-DEC-1995	AMENDMENT	CLINICAL
06-DEC-1995	AMENDMENT	CLINICAL
08-DEC-1995	PHONE CALL	CLINICAL
19-DEC-1995	FDA REPORT	CLINICAL
21-DEC-1995	FDA REPORT	CLINICAL
11-JAN-1996	AMENDMENT	CLINICAL
15-JAN-1996	AMENDMENT	CLINICAL
19-JAN-1996	PHONE CALL	OTHER
29-JAN-1996	AMENDMENT	CLINICAL
30-JAN-1996	AMENDMENT	CLINICAL
06-FEB-1996	PHONE CALL	OTHER
07-FEB-1996	PHONE CALL	OTHER
13-FEB-1996	PHONE CALL	OTHER
14-FEB-1996	PHONE CALL	OTHER
15-FEB-1996	PHONE CALL	OTHER
23-FEB-1996	PHONE CALL	CMC
23-FEB-1996	PHONE CALL	CLINICAL
26-FEB-1996	PHONE CALL	CLINICAL
27-FEB-1996	GENERAL CORRESP TO FDA	CLINICAL
27-FEB-1996	PHONE CALL	CLINICAL
28-FEB-1996	FDA REPORT	CLINICAL
		SAFETY REPORT

COMM DATE	COMM TYPE	DESCRIPTION
28-FEB-1996	PHONE CALL	CLINICAL SAFETY REPORT
01-MAR-1996	FDA REPORT	CLINICAL SAFETY REPORT
04-MAR-1996	PHONE CALL	OTHER TECHNICAL MEETING
05-MAR-1996	AMENDMENT	CLINICAL STUDY
05-MAR-1996	AMENDMENT	CLINICAL STUDY
05-MAR-1996	PHONE CALL	OTHER TECHNICAL MEETING AVAILABILITY
11-MAR-1996	PHONE CALL	OTHER CMC BRIEFING PACKAGE AND TECHNICAL MEETING SCHEDULING
15-MAR-1996	FDA REPORT	CLINICAL SAFETY REPORT
19-MAR-1996	PHONE CALL	OTHER REVIEW
20-MAR-1996	PHONE CALL	OTHER DRUG PRODUCT
20-MAR-1996	PHONE CALL	CMC REVIEW
21-MAR-1996	PHONE CALL	OTHER DRUG SUBSTANCE
22-MAR-1996	PHONE CALL	CMC CLINICAL MEETINGS
25-MAR-1996	PHONE CALL	OTHER DRUG SUBSTANCE
25-MAR-1996	PHONE CALL	CMC FDA FAX CMC MEETING ATTENDEES LIST
27-MAR-1996	GENERAL CORRESP From FDA	OTHER CMC TECHNICAL MEETING AGENDA
27-MAR-1996	GENERAL CORRESP To FDA	OTHER CMC MEETING ATTENDEES; AGENDA;
27-MAR-1996	PHONE CALL	ANNUAL RPT
29-MAR-1996	FDA REPORT	CLINICAL SAFETY REPORT
02-APR-1996	FDA REPORT	CLINICAL STUDY
03-APR-1996	AMENDMENT	OTHER MEETING BRIEFING PACKAGE
05-APR-1996	PHONE CALL	OTHER MEETING BRIEFING PACKAGE
09-APR-1996	PHONE CALL	CLINICAL STUDY
10-APR-1996	AMENDMENT	CLINICAL STUDY
11-APR-1996	AMENDMENT	OTHER MEETING
12-APR-1996	PHONE CALL	OTHER MEETING

COMM DATE	COMM TYPE	DESCRIPTION
15-APR-1996	PHONE CALL	OTHER
16-APR-1996	PHONE CALL	OTHER
18-APR-1996	PHONE CALL	OTHER
18-APR-1996	PHONE CALL	SCIENTIFIC ISSUES
22-APR-1996	PHONE CALL	SCIENTIFIC ISSUES
24-APR-1996	PHONE CALL	SCIENTIFIC ISSUES
26-APR-1996	PHONE CALL	SCIENTIFIC ISSUES
03-MAY-1996	PHONE CALL	SCIENTIFIC ISSUES
06-MAY-1996	PHONE CALL	SCIENTIFIC ISSUES
20-MAY-1996	AMENDMENT	STUDY
20-MAY-1996	PHONE CALL	CLINICAL STUDY
22-MAY-1996	PHONE CALL	OTHER LETTER
24-MAY-1996	FDA REPORT	SAFETY REPORT
24-MAY-1996	PHONE CALL	OTHER LETTER
29-MAY-1996	PHONE CALL	CLINICAL OTHER LETTER
29-MAY-1996	PHONE CALL	CLINICAL OTHER LETTER
30-MAY-1996	PHONE CALL	CLINICAL SAFETY REPORT
03-JUN-1996	FDA REPORT	CLINICAL SAFETY REPORT
04-JUN-1996	FDA REPORT	CLINICAL SAFETY REPORT
04-JUN-1996	FDA REPORT	CLINICAL SAFETY REPORT
07-JUN-1996	GENERAL CORRESP From FDA	FDA RESPONSE TO THE ISSUES
11-JUN-1996	GENERAL CORRESP From FDA	OTHER ACKNOWLEDGEMENT OF BRIEFING PACKAGE
19-JUN-1996	FDA REPORT	CLINICAL SAFETY REPORT
19-JUN-1996	FDA REPORT	CLINICAL SAFETY REPORT
19-JUN-1996	FDA REPORT	CLINICAL SAFETY REPORT
20-JUN-1996	PHONE CALL	OTHER CLARIFICATIONS

COMM DATE	COMM TYPE	DESCRIPTION
24-JUN-1996	FDA REPORT	CLINICAL SAFETY REPORT
01-JUL-1996	AMENDMENT	CLINICAL STUDY
16-JUL-1996	PHONE CALL	CLINICAL STUDY
19-JUL-1996	PHONE CALL	OTHER FOLLOW UP
02-AUG-1996	PHONE CALL	OTHER FOLLOW UP
02-AUG-1996	PHONE CALL	OTHER DISCUSSION
28-AUG-1996	PHONE CALL	OTHER FOLLOW UP
29-AUG-1996	PHONE CALL	OTHER CONTACT PERSON
03-SEP-1996	PHONE CALL	MICROBIOLOGY CLINICAL STUDY
13-SEP-1996	AMENDMENT	OTHER PRE-NDA MEETING AND MICRO REQUEST
20-SEP-1996	PHONE CALL	OTHER MEETING REQUEST
01-OCT-1996	AMENDMENT	OTHER PRE-NDA MEETING
01-OCT-1996	PHONE CALL	OTHER PRE-NDA MEETING
04-OCT-1996	PHONE CALL	OTHER PRE-NDA MEETING
07-OCT-1996	FDA REPORT	CLINICAL SAFETY REPORT
08-OCT-1996	PHONE CALL	OTHER PRE-NDA MEETING
10-OCT-1996	PHONE CALL	OTHER PRE-NDA MEETING
11-OCT-1996	GENERAL CORRESP From FDA	OTHER MEETING MINUTES
11-OCT-1996	GENERAL CORRESP From FDA	OTHER MEETING MINUTES
15-OCT-1996	PHONE CALL	OTHER PRE-NDA MEETING
	PHONE CALL	SAFETY REPORT
16-OCT-1996	PHONE CALL	OTHER PRE-NDA MEETING
18-OCT-1996	PHONE CALL	OTHER CONFIRMATION
21-OCT-1996	PHONE CALL	OTHER PRE-NDA MEETING
22-OCT-1996	AMENDMENT	OTHER BRIEFING PACKAGE
23-OCT-1996	FDA REPORT	CLINICAL SAFETY REPORT

COMM DATE	COMM TYPE	DESCRIPTION
23-OCT-1996	FDA REPORT	CLINICAL SAFETY REPORT
23-OCT-1996	FDA REPORT	CLINICAL SAFETY REPORT
23-OCT-1996	FDA REPORT	CLINICAL SAFETY REPORT
24-OCT-1996	PHONE CALL	CMC DRUG PRODUCT
25-OCT-1996	PHONE CALL	OTHER NDA NUMBER ASSIGNMENTS
25-OCT-1996	PHONE CALL	OTHER
28-OCT-1996	FDA REPORT	CLINICAL SAFETY REPORT
01-NOV-1996	GENERAL CORRESP From FDA	LABEL
01-NOV-1996	PHONE CALL	OTHER SCHEDULE
01-NOV-1996	PHONE CALL	OTHER
04-NOV-1996	AMENDMENT	CLINICAL STUDY
05-NOV-1996	PHONE CALL	OTHER DISCUSSION
06-NOV-1996	GENERAL CORRESP From FDA	OTHER FDA FAX
07-NOV-1996	PHONE CALL	OTHER DISCUSS FDA'S EXPECTATIONS
14-NOV-1996	AMENDMENT	PRECLINICAL PHARMACOLOGY
15-NOV-1996	MEETING MINUTES	OTHER DEMONSTRATION
20-NOV-1996	PHONE CALL	OTHER MEETING MINUTES
20-NOV-1996	PHONE CALL	OTHER SCHEDULING DEMONSTRATION,
26-NOV-1996	GENERAL CORRESP From FDA	OTHER MEETING MINUTES
02-DEC-1996	AMENDMENT	CLINICAL STUDY
12-DEC-1996	GENERAL CORRESP From FDA	MICROBIOLOGY COMMENTS
13-DEC-1996	PHONE CALL	DISCUSSION
16-DEC-1996	PHONE CALL	OTHER
02-JAN-1997	AMENDMENT	STUDY
07-JAN-1997	PHONE CALL	OTHER SCHEDULING DEMONSTRATION

COMM DATE	COMM TYPE	DESCRIPTION
13-JAN-1997	PHONE CALL	OTHER LOGISTICS
14-JAN-1997	PHONE CALL	OTHER LOGISTICS
21-JAN-1997	PHONE CALL	OTHER SCHEDULING CONVERSATIONS
23-JAN-1997	MEETING MINUTES	OTHER MINUTES OF MEETING
23-JAN-1997	PHONE CALL	CLINICAL STUDY
24-JAN-1997	AMENDMENT	CLINICAL SUMMARY
	AMENDMENT	CLINICAL SUMMARY
	AMENDMENT	CLINICAL SUMMARY
27-JAN-1997	AMENDMENT	CLINICAL STUDY
27-JAN-1997	MEETING MINUTES	OTHER MINUTES DEMONSTRATION
27-JAN-1997	PHONE CALL	CLINICAL STUDY
29-JAN-1997	PHONE CALL	CLINICAL SAFETY REPORT
30-JAN-1997	PHONE CALL	OTHER PROVIDIDNG ELECTRONIC FILES
03-FEB-1997	AMENDMENT	CLINICAL STUDY
05-FEB-1997	FDA REPORT	CLINICAL SAFETY REPORT
07-FEB-1997	PHONE CALL	CLINICAL STUDY
18-FEB-1997	PHONE CALL	OTHER SAFETY REPORT
19-FEB-1997	FDA REPORT	CLINICAL STUDY
26-FEB-1997	AMENDMENT	CLINICAL STUDY
19-MAR-1997	AMENDMENT	ANNUAL RPT
02-APR-1997	FDA REPORT	OTHER
10-APR-1997	PHONE CALL	CLINICAL STUDY
11-APR-1997	PHONE CALL	OTHER RESPONSE
11-APR-1997	PHONE CALL	OTHER RESPONSE
14-APR-1997	PHONE CALL	OTHER RESPONSE
16-APR-1997	PHONE CALL	OTHER RESPONSE

COMM DATE	COMM TYPE	DESCRIPTION
18-APR-1997	PHONE CALL	OTHER RESPONSE
21-APR-1997	AMENDMENT	CLINICAL STUDY
21-APR-1997	PHONE CALL	OTHER RESPONSE
22-APR-1997	PHONE CALL	OTHER RESPONSE
28-APR-1997	PHONE CALL	OTHER RESPONSE
01-MAY-1997	PHONE CALL	OTHER
14-MAY-1997	PHONE CALL	OTHER QUESTIONS
15-MAY-1997	PHONE CALL	OTHER QUESTIONS
16-MAY-1997	AMENDMENT	CLINICAL STUDY
16-MAY-1997	GENERAL CORRESP TO FDA	CLINICAL STUDY
16-MAY-1997	PHONE CALL	OTHER QUESTIONS
21-MAY-1997	PHONE CALL	CMC DRUG PRODUCT
23-MAY-1997	PHONE CALL	CMC DRUG PRODUCT
30-MAY-1997	PHONE CALL	CLINICAL STUDY
02-JUN-1997	AMENDMENT	CLINICAL STUDY
03-JUN-1997	PHONE CALL	OTHER SCHEDULING OF TELECONFERENCE
10-JUN-1997	PHONE CALL	CLINICAL STUDY
30-JUN-1997	PHONE CALL	OTHER CONFIRM NDA APPROACH
08-JUL-1997	AMENDMENT	CLINICAL STUDY
09-JUL-1997	AMENDMENT	CLINICAL STUDY
25-JUL-1997	AMENDMENT	CLINICAL STUDY
25-JUL-1997	PHONE CALL	OTHER BRIEFING DOCUMENT
04-AUG-1997	GENERAL CORRESP TO FDA	OTHER STUDY
04-AUG-1997	PHONE CALL	CLINICAL
05-AUG-1997	GENERAL CORRESP TO FDA	CLINICAL
06-AUG-1997	FDA REPORT	CLINICAL SAFETY REPORT

COMM DATE	COMM TYPE	DESCRIPTION
06-AUG-1997	FDA REPORT	CLINICAL SAFETY REPORT
06-AUG-1997	FDA REPORT	CLINICAL SAFETY REPORT
13-AUG-1997	PHONE CALL	OTHER PROVIDING ELECTRONIC FILES ELECTRONIC DELIVERIES.
13-AUG-1997	PHONE CALL	OTHER PROVIDING ELECTRONIC FILES ELECTRONIC DELIVERIES.
13-AUG-1997	PHONE CALL	OTHER PROVIDING ELECTRONIC FILES ELECTRONIC DELIVERIES.
14-AUG-1997	PHONE CALL	CLINICAL STUDY
15-AUG-1997	PHONE CALL	OTHER PROVIDING ELECTRONIC FILES ELECTRONIC DELIVERIES.
20-AUG-1997	FDA REPORT	CLINICAL SAFETY REPORT
02-SEP-1997	PHONE CALL	OTHER PROVIDING ELECTRONIC FILES ELECTRONIC DELIVERIES.
25-SEP-1997	PHONE CALL	CLINICAL STUDY
16-OCT-1997	PHONE CALL	CLINICAL SAFETY REPORT
17-OCT-1997	AMENDMENT	CLINICAL STUDY
29-OCT-1997	FDA REPORT	CLINICAL SAFETY REPORT
04-NOV-1997	PHONE CALL	CLINICAL SAFETY REPORT
05-NOV-1997	FDA REPORT	CLINICAL SAFETY REPORT
19-NOV-1997	AMENDMENT	CLINICAL STUDY
25-NOV-1997	FDA REPORT	CLINICAL SAFETY REPORT
12-DEC-1997	FDA REPORT	CLINICAL SAFETY REPORT
25-FEB-1998	AMENDMENT	CLINICAL STUDY
20-MAR-1998	FDA REPORT	CLINICAL SAFETY REPORT
20-APR-1998	FDA REPORT	ANNUAL RPT CLINICAL SAFETY REPORT
20-APR-1998	FDA REPORT	CLINICAL STUDY
03-JUN-1998	AMENDMENT	CLINICAL SAFETY REPORT
16-JUN-1998	FDA REPORT	CLINICAL SAFETY REPORT
17-JUN-1998	FDA REPORT	CLINICAL SAFETY REPORT

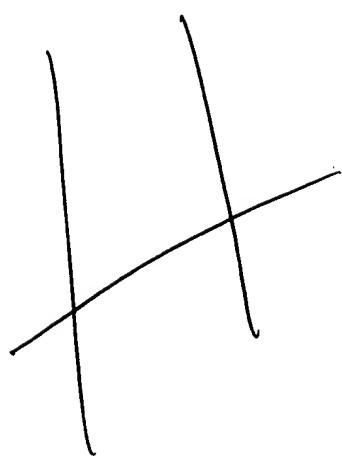
COMM DATE	COMM TYPE	DESCRIPTION
17-JUN-1998	GENERAL CORRESP TO FDA	CLINICAL STUDY
	GENERAL CORRESP TO FDA	CLINICAL STUDY
22-JUN-1998	FDA REPORT	CLINICAL SAFETY REPORT
22-JUN-1998	PHONE CALL	OTHER MISCELLANEOUS QUESTIONS
29-JUN-1998	FDA REPORT	CLINICAL SAFETY REPORT
01-JUL-1998	FDA REPORT	CLINICAL SAFETY REPORT
02-JUL-1998	FDA REPORT	CLINICAL SAFETY REPORT
06-JUL-1998	AMENDMENT	CLINICAL STUDY
10-JUL-1998	FDA REPORT	CLINICAL SAFETY
10-JUL-1998	FDA REPORT	CLINICAL SAFETY
10-JUL-1998	GENERAL CORRESP TO FDA	CLINICAL STUDY
	GENERAL CORRESP TO FDA	CLINICAL STUDY
24-JUL-1998	FDA REPORT	CLINICAL SAFETY REPORT
27-JUL-1998	FDA REPORT	CLINICAL SAFETY REPORT
28-JUL-1998	FDA REPORT	CLINICAL SAFETY REPORT
30-JUL-1998	FDA REPORT	CLINICAL SAFETY REPORT
31-JUL-1998	FDA REPORT	CLINICAL SAFETY REPORT
07-AUG-1998	PHONE CALL	OTHER DISCUSSION
10-AUG-1998	GENERAL CORRESP TO FDA	OTHER
14-AUG-1998	GENERAL CORRESP TO FDA	OTHER
18-AUG-1998	FDA REPORT	CLINICAL SAFETY REPORT
18-AUG-1998	FDA REPORT	CLINICAL SAFETY
24-AUG-1998	AMENDMENT	CLINICAL STUDY
03-SEP-1998	FDA REPORT	CLINICAL SAFETY REPORT
28-SEP-1998	AMENDMENT	CLINICAL STUDY
01-OCT-1998	AMENDMENT	CLINICAL STUDY

COMM DATE	COMM TYPE	DESCRIPTION
01-OCT-1998	FDA REPORT	CLINICAL SAFETY REPORT
02-OCT-1998	GENERAL CORRESP TO FDA	CLINICAL STUDY
12-OCT-1998	FDA REPORT	CLINICAL SAFETY REPORT
13-OCT-1999	PHONE CALL	CLINICAL STUDY
16-OCT-1998	GENERAL CORRESP TO FDA	CLINICAL STUDY
	GENERAL CORRESP TO FDA	CLINICAL STUDY
20-OCT-1998	FDA REPORT	CLINICAL SAFETY REPORT
23-OCT-1998	FDA REPORT	CLINICAL SAFETY REPORT
26-OCT-1998	FDA REPORT	CLINICAL SAFETY REPORT
28-OCT-1998	FDA REPORT	CLINICAL SAFETY REPORT
04-NOV-1998	GENERAL CORRESP	CLINICAL STUDY
11-NOV-1998	AMENDMENT	CLINICAL STUDY
23-NOV-1998	AMENDMENT	CLINICAL STUDY
02-DEC-1998	AMENDMENT	CLINICAL STUDY
04-DEC-1998	FDA REPORT	CLINICAL SAFETY REPORT
29-DEC-1998	AMENDMENT	CLINICAL STUDY
13-JAN-1999	FDA REPORT	CLINICAL SAFETY REPORT
25-JAN-1999	FDA REPORT	CLINICAL SAFETY REPORT
27-JAN-1999	AMENDMENT	CLINICAL STUDY
29-JAN-1999	PHONE CALL	CLINICAL SAFETY REPORT
01-FEB-1999	AMENDMENT	CLINICAL STUDY
01-FEB-1999	FDA REPORT	CLINICAL SAFETY REPORT
02-FEB-1999	AMENDMENT	CLINICAL STUDY
02-FEB-1999	FDA REPORT	CLINICAL CRF SAFETY REPORT

COMM DATE	COMM TYPE	DESCRIPTION
11-FEB-1999	FDA REPORT	CLINICAL SAFETY REPORT
19-FEB-1999	FDA REPORT	CLINICAL SAFETY REPORT
22-FEB-1999	FDA REPORT	CLINICAL SAFETY REPORT
04-MAR-1999	AMENDMENT	CLINICAL STUDY
04-MAR-1999	AMENDMENT	CLINICAL STUDY
09-MAR-1999	AMENDMENT	CLINICAL STUDY
09-MAR-1999	AMENDMENT	CLINICAL STUDY
09-MAR-1999	PHONE CALL	CMC DRUG PRODUCT
10-MAR-1999	AMENDMENT	CLINICAL STUDY
23-MAR-1999	FDA REPORT	CLINICAL SAFETY REPORT
24-MAR-1999	FDA REPORT	ANNUAL RPT
29-MAR-1999	PHONE CALL	LABEL
05-APR-1999	AMENDMENT	CLINICAL STUDY
07-APR-1999	PHONE CALL	LABEL
13-APR-1999	PHONE CALL	LABEL
13-APR-1999	PHONE CALL	LABEL
23-APR-1999	AMENDMENT	CLINICAL STUDY
28-APR-1999	PHONE CALL	CLINICAL STUDY
07-MAY-1999	AMENDMENT	CLINICAL STUDY
10-MAY-1999	PHONE CALL	LABEL
13-MAY-1999	PHONE CALL	CLINICAL STUDY
20-MAY-1999	AMENDMENT	CLINICAL STUDY
20-MAY-1999	PHONE CALL	OTHER NUMEROUS ISSUES
26-MAY-1999	PHONE CALL	OTHER NUMEROUS ISSUES
02-JUN-1999	PHONE CALL	LABEL

COMM DATE	COMM TYPE	DESCRIPTION
07-JUN-1999	AMENDMENT	CLINICAL PROTOCOL AMENDMENT
07-JUN-1999	MEETING MINUTES	CLINICAL STUDY
07-JUN-1999	PHONE CALL	OTHER NUMEROUS ISSUES
10-JUN-1999	PHONE CALL	OTHER NUMEROUS ISSUES
17-JUN-1999	PHONE CALL	CLINICAL NUMEROUS ISSUES
21-JUN-1999	AMENDMENT	CLINICAL STUDY
23-JUN-1999	AMENDMENT	CLINICAL STUDY
	AMENDMENT	CLINICAL STUDY
	AMENDMENT	CLINICAL STUDY
	AMENDMENT	CLINICAL STUDY
24-JUN-1999	MEETING MINUTES	CLINICAL STUDY
24-JUN-1999	PHONE CALL	OTHER NUMEROUS ISSUES
01-JUL-1999	GENERAL CORRESP TO FDA	CLINICAL STUDY
01-JUL-1999	PHONE CALL	OTHER NUMEROUS ISSUES
06-JUL-1999	MEETING MINUTES	CLINICAL STUDY
07-JUL-1999	AMENDMENT	CLINICAL STUDY
07-JUL-1999	AMENDMENT	CLINICAL STUDY
07-JUL-1999	PHONE CALL	OTHER NUMEROUS ISSUES
08-JUL-1999	AMENDMENT	CLINICAL STUDY
13-JUL-1999	AMENDMENT	CLINICAL STUDY
	AMENDMENT	CLINICAL STUDY
15-JUL-1999		OTHER NUMEROUS ISSUES
21-JUL-1999	AMENDMENT	CLINICAL STUDY
22-JUL-1999	PHONE CALL	CMC DRUG PRODUCT

COMM DATE	COMM TYPE	DESCRIPTION
22-JUL-1999	PHONE CALL	OTHER
22-JUL-1999	PHONE CALL	CLINICAL
26-JUL-1999	AMENDMENT	CLINICAL
26-JUL-1999	PHONE CALL	CMC
04-AUG-1999	AMENDMENT	CLINICAL
04-AUG-1999	PHONE CALL	OTHER
06-AUG-1999	AMENDMENT	CLINICAL
06-AUG-1999	AMENDMENT	CLINICAL
09-AUG-1999	GENERAL CORRESP From FDA	CLINICAL
09-AUG-1999	PHONE CALL	OTHER
17-AUG-1999	AMENDMENT	CLINICAL
20-AUG-1999	FDA REPORT	CLINICAL
30-AUG-1999	AMENDMENT	CMC
30-AUG-1999	FDA REPORT	CLINICAL
30-AUG-1999	GENERAL CORRESP To FDA	CLINICAL
31-AUG-1999	PHONE CALL	CMC
08-SEP-1999	AMENDMENT	CLINICAL
13-SEP-1999	FDA REPORT	CLINICAL
14-SEP-1999	AMENDMENT	CLINICAL
16-SEP-1999	AMENDMENT	CLINICAL
	AMENDMENT	CLINICAL
	AMENDMENT	CLINICAL
21-SEP-1999	FDA REPORT	CLINICAL



PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668,669)
Issued: May 26, 1987)
To: Jean-Claude Barriere, Claude Cotrel,)
Jean-Marc Paris)
Assignee: Rhone-Poulenc Rorer S.A.)
For: PRISTINAMYCIN II_B DERIVATIVES)
AND COMPOSITIONS CONTAINING)
THEM)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

CERTIFICATION

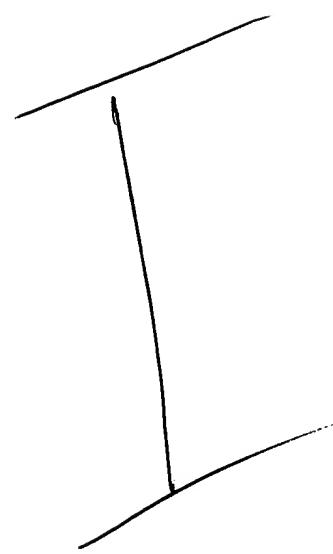
I, CHARLES E. VAN HORN, do hereby certify that this accompanying application for extension of the term of U.S. Patent 4,668,669 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: November 10, 1999



PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668,669)
Issued: May 26, 1987)
To: Jean-Claude Barriere, Claude Cotrel,)
Jean-Marc Paris)
Assignee: Rhone-Poulenc Rorer S.A.)
For: PRISTINAMYCIN II_B DERIVATIVES)
AND COMPOSITIONS CONTAINING)
THEM)

ATTN: BOX PATENT EXTENSION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

**DECLARATION ACCOMPANYING APPLICATION UNDER
35 U.S.C. § 156 FOR EXTENSION OF PATENT TERM**

I, CHARLES E. VAN HORN, do hereby declare:

I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have been appointed as an attorney by the Patent Assignee, Rhone-Poulenc Rorer S.A., with regard to this application for extension of the term of U.S. Patent 4,668,669 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

I have reviewed and understand the contents of the accompanying application being submitted pursuant to 37 C.F.R. § 1.740.

I believe that the patent is subject to extension pursuant to 37 C.F.R. § 1.710.

I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and applicable regulations.

I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: November 10, 1999